NOVEMBER, 1946

NOV 1 1 1946

Vol. 124, No. 5

ANNALS of SURGERY

A Monthly Review of Surgical Science and Practice

CONTAINING PAPERS DELIVERED BEFORE
THE SIXTY-SIXTH ANNUAL MEETING
of the
AMERICAN SURGICAL ASSOCIATION
AT HOT SPRINGS, VIRGINIA
APRIL 2, 3, 4, 1946

Prepared for Publication Under the Direction of
JOHN H. GIBBON, JR., M.D.
Recorder of the American Surgical Association

J. B. LIPPINCOTT COMPANY

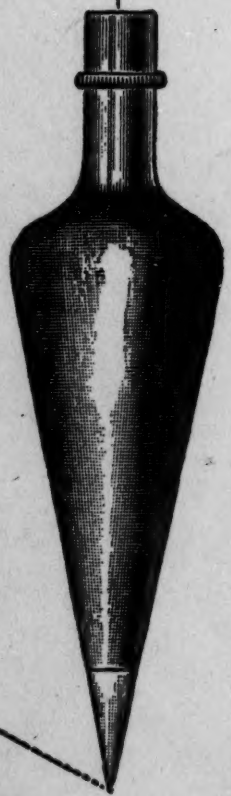
Precision

Of the many types of anesthesia, spinal procedures are the most exacting in their requirements. Because of its pharmacological precision, NEOcaine has demonstrated its fitness for spinal anesthesia over a thirty-year period of clinical use.

In practice, NEOcaine is (1) *always sterile*, (2) virtually flash-soluble in cerebrospinal fluid, (3) stable to epinephrine, (4) rapidly and completely absorbed without irritation and (5) of low toxicity in anesthetic concentrations.

ADMINISTRATION: Employ 1 mg. of NEOcaine per pound of body weight, up to 150 mg. Dissolve crystals with spinal fluid led into the ampoule. Inject slowly with optional barbotage, using a 22 gauge needle. Contraindicated in gastrointestinal perforation, obstruction, peritonitis, severe hypotension, cerebrospinal or dorsal skin disease. Drug idiosyncrasy is rare.

SUPPLIED: Ampoules of 50, 80, 100, 120, 150, 200, 300 mg. of pure procaine hydrochloride. Boxes of 10. For continuous spinal anesthesia, ampoules of 500 mg., individually boxed.



NEOcaine
1917 1946

ANGLO-FRENCH Laboratories, Inc.
75 Varick Street, New York 13, N. Y.

ANNALS OF SURGERY

VOL. 124 NOVEMBER, 1946 No. 5

THE PYRUVIC ACID METHOD IN DEEP CLINICAL BURNS*

GERVASE J. CONNOR, M.D., AND SAMUEL C. HARVEY, M.D.

NEW HAVEN, CONN.

FROM THE DEPARTMENT OF SURGERY, YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN, CONNECTICUT

THE CRUX OF THE PROBLEM, both systemic and local, in the treatment of the severely burned patient, relates to the wound itself. In the treatment of the local area the objective is closure of the wound at the earliest moment compatible with success and with a minimum mortality rate. In the patient with an extensive deep burn this should be the objective of all treatment, beyond the early stages of impending or actual peripheral vascular failure. This concept we believe to be the compelling one from a practical standpoint.

The systemic consequences of the large deep burn are too well known to require recital, but it is pertinent here to note that beyond the first few days after injury the general condition of the patient is determined in large measure by one particular feature of the local area. The profound disturbances in the chemical sphere characteristic of this type of patient are reflections of the *open* condition of the wound. This is strikingly witnessed by the precipitous general improvement in the seriously burned patient when the wound is promptly closed. Clearly, the ultimate problem of the patient as a whole is most directly soluble on the basis of the local area. The solution is prompt *closure* of the wound.

The achievement of this objective in the patient with extensive deep burns poses formidable difficulties, however. The present report deals with one of these specifically, and indicates, in general, its bearing upon the others.

Split skin grafts including a proper thickness of the important derma are preferred for closure in large deep burns. Early skin grafting is a major penultimate goal, therefore, but it is not synonymous with closure of the wound. The chief cause of delay in the early grafting of these wounds is, in effect, the continued presence of the slough. This layer of dead tissue is slow

*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Yale University.

Read before the American Surgical Association, April 2–4, 1946, Hot Springs, Virginia.

to separate and is essentially powerless to combat infection; with it skin grafting is impossible, and contraction continues as long as the wound is open. It is regarded as of signal importance, therefore, to bring about the removal of the slough at the earliest moment. The advantage of this rapid removal is fully realized, however, only when the new surface of the wound is acceptable for immediate skin grafting, and when there is no significant damage to living tissue.

In a previous paper (Connor and Harvey,[1] 1944) we presented a brief summary of a method for the local treatment of deep burns based upon the results of experiments in animals. The central theme of the present report deals with the same method adapted for use in man, and the evidence is based upon clinical data.

Fundamental in these studies is the thesis that the hydrogen ion concentration is an important factor in the healing of the local area in deep burns. The results of preliminary experiments revealed that the separation of the slough can be exceedingly hastened if the *p*H on the surface of the wound is sufficiently lowered, with proper attention to other chemical factors. A large series of organic and inorganic acids were studied for their pertinent effect. Pyruvic acid was found to exhibit outstanding advantages within the recognized objectives of treatment.

METHOD

The following data are descriptive of a general method for the use of pyruvic acid in the local treatment of clinical deep burns.

The stock solution of pyruvic acid is made by adding 7 cc. of pyruvic acid C.P. to one liter of distilled water. The *p*H of the resulting solution should be 1.9.

A content of from eight to ten per cent of cornstarch is desirable in the pyruvic acid starch paste. The exact amount of starch necessary varies somewhat with different commercial brands, but in final consistency the paste should be only semiliquid, permitting easy application. The preparation of the paste is the same whether a large or a small amount is made at one time. The desired volume of stock solution of pyruvic acid is separated into two portions, one (A) of about 20 per cent of the total volume and the other (B) of the remaining solution. Portion (A) is mixed without heating with a calculated amount of cornstarch (8–10 per cent), and thin cold starch paste obtained. Portion (B) is heated to just short of boiling. Portion (B) is then mixed with (A), the cold starch paste, and stirred. With total volumes greater than 400 cc. additional heating with constant stirring for about one minute may be necessary, in order to produce an homogeneous, relatively thick paste. This is then cooled by placing its container in an ice bath. The paste thickens somewhat with cooling.

(Example: If 500 cc. of stock solution of pyruvic acid at *p*H 1.9 is used, about 100 cc. of this is mixed with 50 grams of cornstarch, without heating. The remaining 400 cc. is heated almost to boiling, and the two portions are mixed, stirred, heated a little longer if necessary, and cooled.)

In the use of this method in the treatment of mixed burns certain general points are of great importance and deserve emphasis.

(1) The success of the method depends to a considerable degree upon the *maintenance* of a *thick* layer of active pyruvic acid paste in contact with the wound.

A relatively *large amount* of paste should be applied, to minimize neutralization by the wound fluids. The paste should be applied generously in a thick layer. This is

most readily done by placing the paste on a thin layer of gauze or on a sheet of appropriate size, which is then applied with the paste next to the burn. After application this inner dressing is covered with strips of vaselined gauze or some impermeable dressing so that it does not dry out. For example, in the treatment of a burn involving the entire lower leg, from knee to ankle, about 3,000 cc. of paste is advisable. An excess amount of paste can be used with safety, an inadequate amount is relatively ineffective.

The dressing should be such as to maintain this thick layer of paste in contact with the wound, and to prevent any conspicuous drying out of the paste. Under a properly applied dressing the paste should not dry out between dressings.

(2) Preliminary cleansing or débridement of the wound is unnecessary. In this connection two points deserve notation, the treatment of blisters and the cross-hatching of the slough, but neither of these can be properly classified as "débridement."

(3) Blisters may or may not be opened. In any instance in which the presence of the slough beneath the blister is suspected, and this occasionally occurs, the blister should be unroofed to expose the dead tissue. If this is not done, the treatment will be ineffective in this area.

(4) Separation of the slough by this method proceeds from the margin of the wound. It is therefore highly advisable in large wounds to incise the slough with a scalpel in order to create more "margins." This can be done without anesthesia. The incisions should be carried through the dead tissue in a linear manner.

(5) Areas of first-, second- and third-degree damage can be treated under the same dressing without conversion of the superficial into deep burns.

First Dressing.—The first dressing with the pyruvic acid paste may be performed at any time. In the severely burned patient, in danger of death from peripheral vascular failure, it would appear wise to delay this definitive treatment of the wound in favor of those measures useful in combating the so-called "shock." But the pyruvic acid dressing may be properly applied at once otherwise. In instances in which the local external plasma leakage is excessive, the first dressing may be relatively ineffectual from the point of view of separation of the slough, but this obtains only for a day or two.

Without preliminary cleansing or débridement the dead tissue is incised to provide greater margins, blisters are unroofed if necessary, and the pyruvic acid paste is applied generously in a thick layer directly to the wound. Paste of the proper consistency can be piled in place in many instances. The paste is covered with a thin retaining dressing of dry gauze, which, in turn, is thoroughly covered with large sheets of vaselined gauze or other impermeable dressing to prevent drying. The vaselined gauze has the advantage that, when spread out to include a portion of the adjacent unburned tissues, it helps to anchor the dressing in place and to seal off these edges of the dressing. This is an important feature of the dressing, for properly performed, it is completely adequate to prevent drying out of the paste. This dressing is then covered with a bulky gauze roll and anchored with elastic bandage for security. Splints are incorporated in the outer dressing if necessary, but the best insurance against deforming contractures is early closure of the wound with proper skin grafts.

The application of dressings of pyruvic acid paste to large burned areas on the extremities can be simplified by placing the burned area on a sterile towel, and applying the paste generously to the wound and on the towel; the paste-filled towel is then drawn around the extremity, anchored and sealed with large sheets of vaselined gauze. Such a method insures the covering of the wound with a thick layer of paste, and over it the outer dressing is easily and efficiently applied.

For the treatment of burned areas on the flat surfaces of the body, as the dorsum of the hand and the trunk, the paste is easily held in place within a dam of built-up gauze applied to the greased unburned skin at the margins of the wound. Within this dam of gauze the paste is placed in a thick layer, covered with dry gauze and sealed

with sheets of vaselined gauze. Such a dressing maintains the pyruvic acid in place without drying for several days.

Whenever possible in instances of burns of the extremities, the unburned distal portion of the extremity should be left exposed for inspection. A few preliminary vertical incisions through the slough are good insurance against compromise of the circulation locally from the tourniquet effect of the unyielding eschar.

Pain is irregular in occurrence after these dressings. It is reasonable to expect pain after the application of pyruvic acid directly on a denuded second-degree area, but this has not been invariably the case. The intensity and duration of the pain, when present, are also variable. Although several large burned areas of mixed degree have been successfully treated by this method without apparent pain, it would seem wise to administer codeine or morphine about 15 minutes before at least the first dressing. Various methods have been used for the incorporation of a local anesthetic agent into the pyruvic acid paste, but these have not been refined sufficiently to make them safe in the presence of large wounds.

Subsequent Dressings.—The *p*H of the pyruvic acid paste rises in the presence of the wound fluid, particularly when the external plasma leak is excessive (the first few days after burning) and when the slough has begun to separate. Dressings should be performed at intervals of two to three days, if possible.

When the previously placed dressing is removed the paste should not have dried out, and the entire inner dressing should fall away from the wound without pain. A thin layer of paste usually remains on the surface of the wound; this should be wiped away gently.

The conspicuous change at the first redressing is the *demarcation* of the areas of dead tissue, and this occurs whether the burn extends only into the depths of the derma or into the deeper layers. In fresh burns there may be little gross evidence of separation at this time; in older burns the edges of the slough may show obvious separation.

Whether or not débridement is combined with the use of pyruvic acid at redressings (see below for discussion) the new dressing is applied in a manner entirely similar to that used in the previous one, a generous application of paste being used.

At the second redressing in large third-degree burns beginning separation of the slough should be apparent. It is at this time that débridement according to a particular technic is of great value, for the demarcation of the slough in both the vertical and horizontal planes will be obvious.

In third-degree burns not involving tendons or thick fascia the wound should be ready for split grafting within a week or slightly longer. The new base of the wound should consist of well-vascularized early granulation tissue. If grafting must be delayed momentarily, the wound may be dressed with a small amount of the pyruvic acid paste.

Deep Second-degree Burns.—Areas in which the damage extends only into the depths of the derma, with preservation of deep epidermal islands but with a covering of slough, should receive the same treatment as deeper areas. When the cleavage plane is within the derma, an additional 48 hours may be required for complete separation of the dead tissue. When such separation has taken place, however, the wound should heal promptly, if sufficient epidermal islands are present. In such instances healing is often surprisingly rapid when the slough is speedily removed without clinical infection, even though the layer of dead tissue is relatively thick.

"Débridement."—The early demarcation of the slough and consequent definition of the proper cleavage plane with this treatment permits a valuable modification of the method. This consists in the use of "débridement" together with pyruvic acid at the time of the redressings. The term "débridement" is employed rather loosely in this connection since the maneuver is used merely to hasten, but not to complete at one sitting, the separation of the slough.

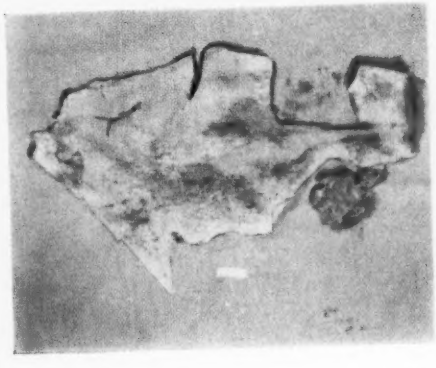
FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 5



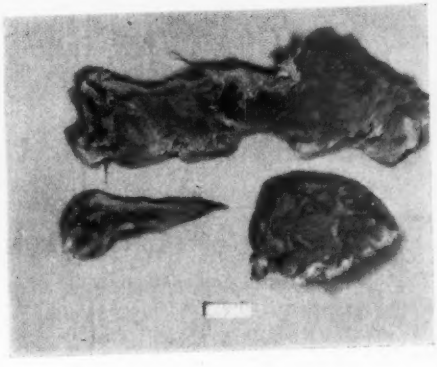


FIG. 6

PLATE I

FIGS. 1 and 2.—Case 1. A. C.: Separation of the slough in one piece through the development of a cleavage plane beneath it (see text).

FIGS. 3–6.—Case 2. J. K.: Severe electrical burn of arm and leg, to show rapid separation of the slough and clean granulating wound (see text).

Although separation of the slough proceeds with the use of the pyruvic acid paste alone, the process can be materially hastened with safety when the demarcated plane of cleavage is developed by sharp dissection for a few centimeters beyond the established limits of complete separation. This is true *even though the cleavage plane is within the derma,* and sufficient residual epidermal elements are present. The safety of this maneuver is dependent upon the fact that the proper plane of cleavage is sufficiently defined by demarcation of the slough to be obvious grossly, and that a zone of incomplete separation often lies among the areas of complete separation. For example, in a large deep burn at the end of four days of treatment the slough may have separated at the edges so that elevation of these margins reveals only vertical strands of dead connective tissue anchoring the slough to its base, with many large and small intervening areas of complete separation. When these anchoring strands of slough are divided, bleeding is absent and the cleavage plane is further developed, so that the subsequent application of pyruvic acid reaches the more remote areas under the residual slough. This extension of the line of cleavage, surgically, should properly extend inward only to the point where demarcation is entirely clear, if the destruction of residual epidermal elements and bleeding are to be avoided.

Stronger Stock Solution.—When there is no question of preservation of residual epidermal islands, the strength of the stock solution may be increased to 9 cc. of pyruvic acid per liter of distilled water, until the slough has separated.

When the slough includes dense tissue or tendons, separation is considerably hastened when débridement by the above technic is employed in addition to pyruvic acid.

RESULTS

More than 30 cases have been treated in this manner, many of them with multiple wounds. The results have been similar to those previously described in the experiments in animals. The layer of dead tissue separates rapidly, and living islands of skin survive in those areas in which the full-thickness of the skin has not been destroyed in the burning. The deep wounds are then acceptable for immediate grafting, and in the more superficial wounds the islands of viable epidermis regenerate. All areas of the mixed clinical burn may thus be treated under the same dressing.

The manner of separation of the slough under these circumstances is of great significance. This is strikingly apparent in the experimental wound and is equally clear in the clinical cases. Separation appears to begin at the margin of the slough and to proceed centrally through the development of a plane of cleavage beneath the dead tissue. The slough separates in large sheets. It is clearly apparent that the slough itself is not digested. This is well-illustrated in the following case, and in Case 4:

Case 1.—A. C., a white male, age 50, sustained deep burns of the thighs in attempted suicide, and was admitted to the hospital in critical condition from carbon monoxide poisoning. The wounds were treated with vaselined gauze and pressure dressings. After 20 days the slough had failed to separate and was firmly adherent in all areas, even at the margins. A dressing of pyruvic acid was first applied at this time. The proximal few centimeters of the wound on each thigh was left *untreated,* except for a minimal amount of paste which leaked onto this area. The remainder of the wound was completely covered with a thick layer of paste.

The dressing was changed three days later. The slough had separated markedly in many peripheral areas but was firmly attached proximally. Pyruvic acid paste was again applied in a thick layer.

Six days after the initial treatment by this method the slough had completely separated except for a thin proximal band (Fig. 1). The slough lay on the surface of the wound and could be lifted free, hinged proximally (Fig. 2). The separated layer of dead tissue itself was rubbery and intact in a single sheet on each wound. The granulating surface of the wound was clean and highly vascular, but there was no bleeding from it. At the margins of the wound there were several areas of viable deep derma. The surrounding skin was uninjured.

The granulating wound was successfully closed with split grafts. In the areas of exposed deep derma at the margin epidermal islands promptly regenerated, but in the remainder of the wound the damage was of third-degree.

This case illustrates particularly well the separation of the slough through the development of a cleavage plane beneath it. The slough itself was not digested. With this treatment it is clear that separation begins at the margin. In this case the margins of the wounds were relatively large compared to the area of the slough, and the slough was purposely not incised to create more margins. In circumferential deep burns of the extremities the margins of the wound may be exceedingly small (Case 4); under these circumstances there is a great advantage in a few linear incisions through the dead tissue in order to provide a relatively large "margin."

Preparation of the local area in the large deep burn for grafting within a period of even a month is often regarded as efficient treatment in clinical practice. With proper application of the pyruvic acid method the usual large deep thermal burn should be ready for successful grafting within a period of ten or 12 days, often in less time. Smaller burned areas should be prepared within a proportionately shorter period, approaching that previously noted in the experimental deep burn.

The surface of the wound is exceptionally vascular after separation of the slough by this method, but there is no bleeding. When the treatment is begun at an early date, and is intensive, this new surface of the wound may have the general appearance of pink subcutaneous tissue; histologically, it is early granulation tissue. The edges of the wound are sharp and clean.

Severe electrical burns are commonly regarded as particularly destructive and troublesome. They would appear to be an adequate testing ground for the efficiency of a method of local treatment. Many of the features of the present method are shown in the following case:

CASE 2.—J. K., a white male, age 51, sustained severe electrical burns of the arm and legs from prolonged contact with a high tension wire. The wounds were treated initially in another hospital with a thin dressing of sulfonamide cream. This, and a dressing of vaselined gauze, were the only local treatment for two days.

Two days after burning, and before the first dressing with pyruvic acid paste, the local areas revealed evidence of marked destruction (Figs. 3 and 4).

The soft tissues of the arm (Fig. 3) were completely divided down to, and exposing, the humerus just above the elbow. A wrist drop was present. This arm had supposedly hung sputtering over the high tension wire. When the divided muscles which filled this groove were separated, a charred mark about 2 cm. in diameter was viable in the humerus itself, and this bone was bare over two-thirds of its circumference for a distance of about 5 cm. The adjacent tissues upward and downward from this groove were the site of a rubbery, insensitive slough which was firmly

FIG. 7

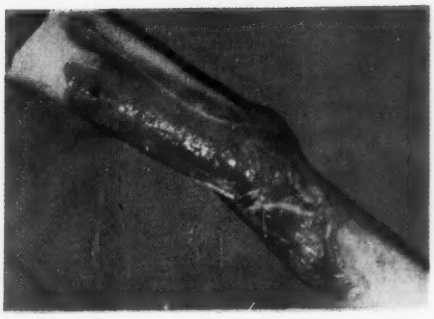


FIG. 8

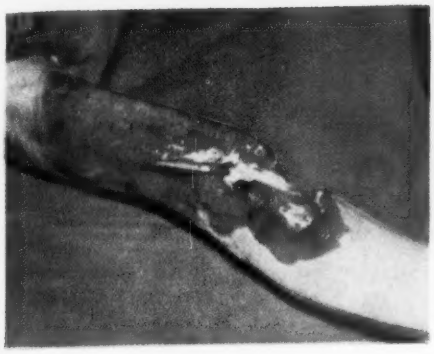


FIG. 9

FIG. 10

FIG. 11

FIG. 12

PLATE II

FIGS. 7–9.—Case 2. J. K.: Severe electrical burn of arm and leg, to show rapid separation of the slough and clean granulating wound (see text).

FIGS. 10–12.—Case 3. E. E.: Deep second-degree burn, to show prompt separation of slough with preservation of viable epidermal islands (see text).

adherent. A large patch of gray similar tissue extended medially across the antecubital space.

A similarly destructive injury was present over the left thigh, popliteal space and lower leg (Fig. 4). Here, again, the soft tissues had been divided in the burning down through the muscle. The tibia was exposed just below the knee for a distance of about 2 cm. The remainder of the burned area was covered with a layer of rubbery gray tissue which was firmly adherent. A drop foot was present.

On the opposite thigh (right) was a smaller area of damage without actual division of tissue. This was covered also with a layer of adherent, insensitive slough.

In view of the nature of the burning agent (electricity) and the actual division of tissue under these circumstances it was suspected that the damage was even more extensive than it appeared to be.

The pyruvic acid treatment was started at this time, two days after burning. Edema had become marked in the unburned tissues distal to the burn. A linear incision was made in the unyielding slough over the arm and over the popliteal space without anesthesia. All of the wounds were treated simultaneously, and a thick layer of pyruvic acid paste was applied.

The dressings were changed at the usual intervals of a few days. Large areas of slough promptly separated in sheets, some of which are shown in Figures 5 and 6. The slough of skin and subcutaneous tissue which came away from the knee and thigh was more than 0.5 cm. in thickness in several areas (Fig. 5). In addition, sections of muscle at least 6 cm. in thickness (Fig. 6) separated in one piece from the walls of the original grooves in the arm and leg. The slough itself was not digested, and separation had taken place through the development of a cleavage plane beneath it.

Thirteen days after the first pyruvic acid dressing all of the wounds were free of slough and in excellent condition (Figs. 7, 8 and 9). The vascularity of the exposed tissues characteristic of this treatment was marked, but there was no bleeding from them. In the right arm (Fig. 7) the humerus was exposed for several centimeters. The bone here appeared a dead grayish-white in color and presented the previously noted blackened area in it. The edges of the wound were sharp and clean. In the left leg (Figs. 8 and 9) the wound was essentially similar to that in the arm. Tendon and fascia were exposed around the knee, but these tissues appeared to be viable. The tibia was exposed as already noted.

The soft tissue wounds were covered with thick split grafts which survived for closure of the defect in these tissues.

The utility of this method of treatment would be seriously reduced if with its use residual epidermal islands within the wound were necessarily destroyed. This is not the case, however, for in those burns in which the serious damage extends only into the derma, but with preservation of residual epidermal islands, separation of the slough proceeds so as to permit regeneration of these islands. The cleavage plane develops within the derma at the appropriate depth.

This emphasizes an important feature of the method. In the standardization of the procedure for practical application the concentration of pyruvic acid was chosen with this consideration. When there is no need for preservation of these deep epidermal islands a stronger solution of pyruvic acid may be used, with even more rapid separation of the slough. The usual clinical deep burn is a mixed one, however, with at least small areas of more superficial damage. In repeated instances in the present series of cases numerous viable epidermal islands have been present after separation of a thick slough

by this method. The method was standardized with a view to the preservation of these deeper epidermal islands. All areas of the mixed clinical burn may thus be treated under the same dressing without fear of converting the superficial injury into a deep one.

A conspicuous feature of this method is the early *demarcation* of the slough in questionable areas. In fresh burns it is often difficult to determine with accuracy in the beginning the extent of the layer of dead tissue.

The following case illustrates the separation of the slough in a wound in which deep epidermal islands were viable. Although the area in question is small, this case was chosen as particularly suited to illustrate the point. The small local area was intensively treated from the beginning, and when the slough had separated, the exposed surface of deep derma was further treated with the same pyruvic acid paste. This additional treatment is not recommended, as other agents are better adapted for use once the local problem involves only epithelization from islands within the wound.

CASE 3.—E. E., a white female, age 26, sustained a burn of the upper and lower arm when her sweater caught on fire. The burning was of short duration. She came to the hospital within a half hour after injury.

The entire arm was burned. Most of the local area appeared to be only superficially injured, however, with many intact and collapsed blisters. There was one grayish area on the inner aspect of the upper arm near the elbow (Fig. 10), suggesting somewhat deeper damage.

The entire burned area on the arm was dressed with a thick layer of pyruvic acid paste. The patient reported (on questioning) a slight local twinging sensation for about five minutes, but refused medication.

Two days later there was conspicuous demarcation of the slough on the grayish area previously noted (Fig. 11), but there was no gross evidence of separation. The adjacent blistered area appeared undamaged. Pyruvic acid paste was again applied, and medication for pain was not required.

Three days later the slough had markedly loosened but had not completely separated. When its edge was lifted, however, it was apparent that only a few soft dermal strands held it in place. The layer of dead tissue was peeled away at this time, like wet paper from glass. There was a slight hang at only one point near the center. The separated slough was intact (Fig. 12) and showed no evidence of digestion. The surface of the wound exposed after separation of the slough appeared to contain deep dermal tissue (Fig. 13) and was clinically clean.

This wound, free of slough, was treated for an additional five days with a thin layer of pyruvic acid paste. Numerous epidermal islands in the base of the wound regenerated in spite of this treatment, and the entire wound was completely epithelized one week later. The patient failed to return for photography but was finally induced to do so, one month after burning (Fig. 14).

The impression that superficial burns (without a significant covering of dead tissue) form an adequate testing ground for the efficiency of method for the local treatment of burns in general is a mistaken one, and has led to waves of enthusiasm for procedures which fail to prove their advantage in the presence of slough. We wish to note, therefore, that Case 3 has been cited only for the specific purpose of illustrating the safety of the pyruvic acid method in this type of injury.

FIG. 13

FIG. 14

FIG. 15

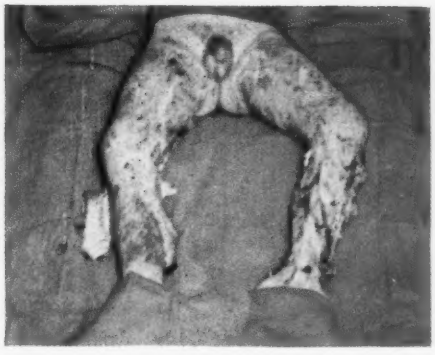


FIG. 16

FIG. 17

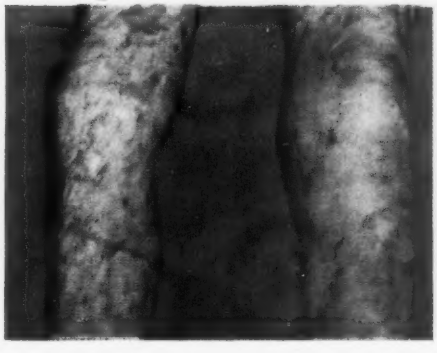


FIG. 18

PLATE III

FIGS. 13 and 14.—Case 3. E. E.: Deep second degree burn, to show prompt separation of slough with preservation of viable epidermal islands (see text).

FIGS. 15–18.—Case 4. J. V.: Severe deep burn by fire, to show rapid separation of slough in sheets, clean granulating wound acceptable for prompt closure with split grafts, immediate and late results of grafting (see text).

The full advantage of the rapid removal of the slough is realized only when the wound is acceptable for immediate skin grafting and is promptly closed, even though it is extensive. When the entire large deep burn is rapidly prepared for grafting, the gain is only a relative one unless the open wound is promptly converted into an essentially closed one. As has already been noted, this concept we believe to be the cogent one from a practical standpoint.

The clean vascular surface exposed in deep burns after separation of the slough by this method is admirably suited to support a covering of living skin, regardless of the presence of bacteria as indicated by culture. This is true even in the deep burn which is clinically infected when the pyruvic acid treatment is begun (see Case W. T., Connor and Harvey,[1] 1944). It is probable that few bacteria multiply and that many will not survive at the concentration of hydrogen ions present in the pyruvic acid paste. The more important factor in the survival of the skin grafts is believed to be the highly vascular clean surface of the wound, since bacteria are regularly obtained upon culture of this area.

It is understood that the rapid closure of the extensive deep burn free of slough poses serious difficulties. The various ramifications of this aspect of the problem are widespread, but it is pertinent to note here that the pyruvic acid method attains real significance in direct proportion to the speed with which the prepared open wound is converted into an essentially closed one.

The following case illustrates the relationship of the pyruvic acid method to the general problem in severe deep burns:

CASE 4.—J. V., a white child, age eight, was admitted to the hospital a half hour after having sustained a severe burn of both entire lower legs when his clothes caught on fire. There was some delay in extinguishing the fire since he had oil on his trousers. His left stocking was rolled down around the ankle and was also oil-soaked.

At the time of admission to the hospital both lower extremities were circumferentially burned. A linear incision was made in the unyielding charred skin to avoid constriction. A conspicuous ring of gray tissue was present around the left ankle at the level of the malleoli, this being notable in view of later developments. The greater part of both lower extremities appeared seriously damaged.

Intensive measures to combat peripheral vascular failure were instituted, and a pressure dressing was applied over vaselined gauze without preliminary cleansing.

Three days later the patient's general condition was satisfactory and the first dressing of pyruvic acid was applied, 6,600 cc. of paste being used for both lower extremities. The burned areas were little changed (Fig. 15) and were incised with a scalpel, linear and transverse incisions several centimeters apart being made to create more margins before the dressing was applied. The wound was not cleansed or débrided.

Two days later the slough had begun to separate. A dressing of pyruvic acid paste was again applied to both lower extremities.

Three days later (eight days after admission, five days after first dressing with pyruvic acid paste) much of the slough was hanging loose or had completely separated in a large sheet, and most of the remainder of the slough was held in place only by soft strands (Fig. 16). It was clear that a cleavage plane had developed beneath the slough which was still in place, and that the separated slough was without evidence

of digestion on its surface. The separated slough, which hung loose in sheets, was cut free from the incompletely separated dead tissue. Pyruvic acid paste was again applied.

Two days later (ten days after admission, seven days after the initial pyruvic acid dressing) the wound was free of slough and acceptable for grafting. The patient developed serum sickness (tetanus antitoxin administered on admission) which lasted for only a few days. There was considerable difficulty in securing compatible blood donors, the patient being *Rh-negative.* Extensive grafting was planned for the first operation, and intensive efforts were made to bring the patient's general condition to a high level to permit this. An exceptionally high protein diet was administered and the daily urinary output was maintained at about 2,000 cc.

Five days later (12 days after initial pyruvic acid dressing) sufficient compatible *Rh-negative* blood was available, and the wounds were in excellent condition. There were several striking features of the burned areas at this time. The surface of the wound was clean and highly vascular without bleeding (Fig. 17). The deepest damage was at the ankle on the left side. Both malleoli were exposed over an area of more than a centimeter in diameter, the joint space was widely open medially and laterally; the Achilles tendon, the peroneal and extensor tendons at the ankle were also exposed. These tendons appeared to be in good condition otherwise.

On this day the wound was extensively covered with split grafts, these being secured from both buttocks, the lower back on each side, both shoulders, both sides of the anterior abdominal wall and the anterior chest. About 200 square inches of skin was grafted at this one operation. Donors for homografts had been kept in readiness but were not used since the patient withstood this extensive procedure well. The granulating areas over the knees and popliteal spaces, and the exposed tendons were covered first, since these were of the greatest importance from a functional standpoint; the exposed tendons were grafted directly. All the available skin grafts were used without accurate patching, since skin was at a premium for complete coverage of the large granulating areas.

The grafts took well in all areas, including those over the Achilles tendon and extensor tendons. Intensive general treatment was continued to permit successive operations for closure of the wound as soon as possible.

Seven days after the original skin grafting, additional split grafts were taken from the skin in the axillae and over the lateral aspect of the chest and buttock on each side as well as from part of one of the *previous donor sites,* permitting further closure of the wound. Again, effort was made to conserve skin and small areas were left between the grafts in some places. The previous grafts had taken around the malleoli which had been exposed, but this bone was now covered with granulation tissue, which was covered with small grafts at this operation. The patient tolerated this procedure well.

Five days later (12 days after the first grafting), much of the wound was covered with living split grafts with an adequate dermal pad (Fig. 18). Greatest attention had been given to the knees, and the grafts here were placed close together. Patchy areas of granulation tissue were apparent where the grafts otherwise had been spread for greatest coverage but without too much regard for small areas between them.

In addition to these small areas there remained one large area on the posterior aspect of the upper thigh on each side and one on the lower leg, yet to be grafted. Most of these were covered on this day with sheets of skin obtained from *three of the original donor sites which had now healed.* The original grafts taken from these areas were used to cover the knees and contained about one-half of the derma.

Thirty days after the first pyruvic acid dressing (33 days after admission) the wound was essentially closed (Fig. 19). There remained only a few scattered granulating areas in between the grafts which had been placed for greatest coverage without accurate patching. Three small areas were closed with bits of split grafts in order

FIG. 19

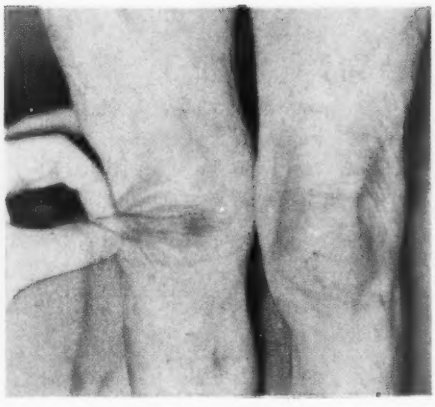


FIG. 20

FIG. 21

FIG. 22

PLATE IV

FIGS. 19–22.—Case 4. J. V.: Severe deep burn by fire, to show rapid separation of slough in sheets, clean granulating wound acceptable for prompt closure with split grafts, immediate and late results of grafting (see text).

to improve the ultimate functional result, although most of them would probably have epithelized rapidly.

Fifteen months after the original injury the local areas were all in excellent condition (Figs. 20, 21 and 22). There were no contractures, the transplanted skin was durable and freely movable (Fig. 20), especially over the important area of the knees. There was no palpable deep scarring except over the left ankle where, it will be recalled, the joint space had been widely open and many of the supporting ligaments destroyed. This joint had become dislocated and there had developed evidence of a local epiphysitis. The functional result was otherwise excellent.

SUMMARY

The results in clinical cases of deep burns treated by the pyruvic acid method support those obtained with similar treatment of experimental burns in animals. The slough separates rapidly without significant damage to living tissue, and the wound is immediately acceptable for extensive skin grafting regardless of the presence of bacteria as indicated by culture. The ultimate objective of treatment in deep burns, namely, the early closure of the wound, can thus be speedily achieved.

The authors wish to express their appreciation to Dr. Philip B. Cowles of the Department of Immunology, Yale University, for his invaluable assistance in this study.

Acknowledgment is due to Miss Mildred Konick for the photography.

REFERENCE

1 Connor, G. J., and Harvey, S. C.: The Healing of Deep Thermal Burns: A Preliminary Report. ANNALS OF SURGERY, **120**, 362–366, 1944.

DISCUSSION.—DR. JOHN STAIGE DAVIS, Baltimore, Md.: I had not intended to say anything tonight, but I cannot resist speaking about this last paper. The method has apparently solved the problem of disposing of deep burn sloughs, which is something we have been struggling with for years, and to which we have never previously had a satisfactory answer. The results shown are remarkable, and I think pyruvic acid is going to make a great difference hereafter in the treatment of burns. I congratulate Doctors Harvey and Connor on this splendid piece of work.

DR. OLIVER COPE, Boston, Mass.: All of us who have had the privilege of going to New Haven and seeing some of Doctor Connor's patients have been much impressed by the extraordinary change created by pyruvic acid paste. I have reservations regarding the exact rôle of the *p*H of the paste. There are properties other than the *p*H which may help along the way. Doctor Connor has not told us all of his tricks; he is adept at making epithelium sprout by changing from pyruvic to succinic acids.

Doctor Lund's paper, and the work his group has been doing has been of enormous interest to other workers in government research projects in this field. Vitamin C is interwoven with the alarm reaction and it and other vitamins may be involved in the reaction of the patient to infection. It has been of great interest and help to us to have seen their work.

In the absence of Doctor Moore, I would like to allude to our work. The methods which Doctor Moore has developed using radioactive isotopes are magnificent tools but, after all, the value of tools is the result and knowledge obtained with them. Doctor Moore has been able to tell us a lot, but we do not pretend to know all the answers regarding the massive red cell destruction in deeply and extensively burned patients.

DR. C. C. LUND, Boston, Mass.: I want to add my congratulations to Doctors Harvey and Connor. I admit I have been doubtful for a long time over the reports of the chemical débridement of burns, but I am now very thoroughly convinced, and feel I have been a little slow. I have not had any practical experience on the subject to bring to you. Of course, when it comes to deciding between chemical débridement and surgical débridement, both are advances, and both may find a permanent place in surgery, but nobody has yet reported on the comparative use of both methods in the same clinic. Doctor Cope's paper concerns a study of anemia by technics that our group has not used. However, anyone handling burns must be faced with the very serious problem of anemia. Formerly, it was generally believed that sufficient transfusions to keep the patient's hemogoblin in the neighborhood of 70 per cent was adequate treatment. Our patients have been much better when we have maintained the hemoglobin above 90 per cent.

DR. SAMUEL C. HARVEY, New Haven, Conn.: I would be regretful if this demonstration had deflected attention away from the work of Doctor Cope and Doctor Lund. There remains to be learned a great deal from these two papers, because we still will have, under the most favorable circumstances, suppurative wounds and the problems of metabolic deficiencies and anemia.

Doctor Connor deserves the entire credit for this work. It has been accomplished only by his most painstaking care of these patients. The details have not been given because of lack of time, nor has it been possible to consider the many other patients. These two cases were selected because they demonstrated instances which usually give rise to serious problems. I hope other clinics will feel inclined to try this procedure. A criticism has been made that it takes too much time. It does take a lot of time, but if one considers the length of time it takes to care for patients who otherwise remain in the hospital for many months, I think the credit is in favor of this more concentrated type of treatment.

DR. GERVASE J. CONNOR, New Haven, Conn. (closing): We wish to thank you for your kind remarks, and to Doctor Cope and Doctor Lund I may say that the respect is mutual. There is one word I should like to add. We may have left partly the wrong impression, since the pyruvic acid method has received the major emphasis in this discussion.

The proper objective in the treatment of large, deep burns is prompt closure of the wound. The pyruvic acid method becomes merely an improved means to a relatively unimproved end unless the prepared wound is promptly closed. The general condition of the patient is determined, in large measure, by the *open* condition of the wound. The problem of the patient, as a whole, is most directly soluble on the basis of this one fact. The solution is prompt closure of the wound.

THE ANEMIA OF THERMAL BURNS*

FRANCIS D. MOORE, M.D., WENDELL C. PEACOCK, PH.D.,
ELIZABETH BLAKELY, A.B., AND OLIVER COPE, M.D.

BOSTON, MASSACHUSETTS

FROM THE DEPARTMENT OF SURGERY OF THE HARVARD MEDICAL SCHOOL; AND THE SURGICAL SERVICES AT THE MASSACHUSETTS GENERAL HOSPITAL; AND THE RADIOACTIVITY CENTER OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, BOSTON, MASS.

ANEMIA has become acknowledged as a common complication of any extensively and deeply burned patient who survives the period of burn shock. The anemia is progressive and is accompanied by debility. It may be so severe that the wounds will not heal unless massive transfusions of whole blood are administered.

The magnitude of the problem of anemia following severe burns is illustrated by the number of transfusions given to four patients before healing was achieved (Table I). These patients were treated in 1943, before the present study was initiated, and, indeed, served as a stimulus for the study. Two of the four patients (Cases 41 and 131)† entered this hospital 8 and 20 months, respectively, after injury, with extensive unhealed granulating wounds of the legs. Both patients were anemic, hypoproteinemic and emaciated. The other two (Cases 13 and 116) entered immediately following their injuries but were unwittingly allowed to become anemic and malnourished before red cell transfusions were started. None of these four patients was treated by expeditious closure of their full-thickness wounds. The necrotic slough was allowed to separate spontaneously, exposing open infected wounds. All were treated with sulfonamides and without penicillin. Numerous skin grafts elsewhere had been unsuccessful in the first two patients. Successful grafting in all was achieved only late after the injury, when the anemia and malnutrition had been partially relieved. The amounts of whole blood given these patients were minimal, certainly not optimal, since all four patients left the hospital with residual anemia and hypoproteinemia.

The origin of the anemia of burns was ascribed, in 1942, by Altemeier and Carter[1] to external loss of blood from the infected granulations. More recently, the frequency with which gross hemolysis and massive hemoglobinuria have

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

This work was also aided by a grant from the Ciba Pharmaceutical Products, Inc., Summit, N. J.

Read before the American Surgical Association, April 2-4, 1946, Hot Springs, Virginia.

† The same case numbers are used in all articles on burn patients studied at this hospital under contract with the Committee on Medical Research. Numbers 1 through 39 refer to the Cocoanut Grove fire cases, numbers 40 through 96 to cases studied before the Cocoanut Grove fire, and numbers 97 through 278 to cases studied since the Cocoanut Grove fire.

been encountered in the hours immediately following injury has called attention to an early destruction of red blood cells, allegedly due to the heat itself. Shen, Ham, and Fleming[2] have disclosed an early increased fragility of the red blood corpuscles. The Burns Unit in England, under Colebrook,[3] has extended this observation to find that by 18 hours all the fragile cells have disappeared from the circulation, leaving only the stable cells or those with decreased fragility.

In addition to the observed losses of red cells by hemorrhage from the wound surface and by hemolysis, other causes of a decrease in circulating red cell mass might be postulated. The administration of large volumes of plasma in the therapy of burn shock could theoretically give rise to destruction of cells if the plasma pools contained an excess of anti-A or anti-B agglutinins. Red cells may be destroyed at the inflammatory barrier of the infected wounds; Menkin[4] has shown a deposition of iron in this area. Wintrobe and his coworkers[5] have suggested that such a deposition may be the reason for deviation of iron from the bone marrow. They have observed hypoferremia associated with an anemia

TABLE I

THE PROBLEM—1943

TRANSFUSIONS GIVEN TO FOUR PATIENTS WHO WERE DISCHARGED WITH HEALED WOUNDS BUT WITH RESIDUAL ANEMIA

Case Number	Extent Full-thickness Burn	Whole Blood Transfusions	Duration of Hospitalization
41	20%	4,500 cc.	5 months*
131	15%	6,500 cc.	8 months†
13	28%	12,500 cc.	4 months
116	12%	2,500 cc.	6 months

* Burned 8 months prior to admission to this hospital.
† Burned 20 months prior to admission to this hospital.

refractory to iron therapy in patients with acute and chronic infection. It is also possible that toxins of infectious origin might suppress the regenerative activity of the bone marrow by means other than iron deviation.

These observed and postulated causes of anemia in the burned patient should all create a true anemia, or decrease in circulating red cell mass, which should be differentiated from the false anemia due to an increase in plasma volume resulting in red blood cell dilution. Such a false anemia has been shown to follow soon after the initial period of hemoconcentration. Studies of the redistribution of fluid within the extracellular space at this hospital,[6] and elsewhere,[7] have shown that once the interstitial or extravascular compartment of the extracellular space has been stretched to the maximum such an enlargement of the plasma volume may occur. This enlargement may be produced either by continued fluid therapy in excess of renal output or by beginning mobilization of fluid from the overdistended interstitial space. Clinically, such a fluid shift is recognizable as subsidence of edema which usually starts about 48 hours after the injury; if the wounds are extensive, blood dilution may persist for several days in spite of a large renal output.

The stubborn and disabling character of the anemia has prompted this investigation. We have strived to determine: first, the significance of the observed and postulated causes of the burn anemia; second, how far the customary methods of measuring an anemia suffice for the guidance of therapy and to what extent newer methods of blood volume determinations must be introduced as a clinical routine; and, finally, to record the relative expense in terms of red cells required under different modes of therapy. The expense of treating an established anemia has already been observed (Table I).

METHODS

Studies of the peripheral blood alone may provide an approximation of the extent of an anemia. However, if whole blood is continually lost and dehydration is present, so that refilling of the plasma volume from the extracellular fluid is abnormally slow, hematocrit, hemoglobin, or red cell counts in the normal range may theoretically coexist with striking reductions in the circulating red cell mass. For this reason, as well as a desire to quantitate the loss, one must go beyond a description of the peripheral findings and measure the circulating red cell mass and the changes in this red cell mass after the burn.

Of the methods available to study the red cell mass, the simplest is a measurement of the dye plasma volume and a calculation of the red cell mass from the hematocrit. This method suffers from some systematic error traceable to the fact that the large vessel hematocrit is somewhat larger (about 10 to 15 per cent) than the whole body hematocrit.[8] However, this fault is not insurmountable if the same method is used for serial determinations and there are no acute changes in body fluid metabolism which alter the relationship between the whole body hematocrit and the peripheral hematocrit during the course of the study. The method is also affected by widespread alterations in capillary permeability and presence of other pigments in the serum.

A method which measures the red cell mass directly would be preferred and we have used a measurement of the patient's red cell mass by the injection of red cells containing radioactive iron and a quantitation of the dilution of these injected cells using physical measurements of the radioactivity.*[9,10]

In brief, this technic involves the preparation of radioactive red cells in a donor by the injection of the five-year half-life isotope of iron (as ferric ammonium citrate), over a period of two or three weeks. At the end of this time the activity of the donor may be determined and when it is sufficient to allow measurement of his cells diluted in the patient's cells, the build-up is ceased. At a time when the red cell mass of a patient is to be measured, the radioactive donor is bled of 100 to 500 cc. of blood into citrate and this amount is injected into the patient after careful measurement of the hematocrit of the injected blood. The radioactivity per cubic centimeter of cells in the donor blood, and

* In expressing the results in the figures the red cell volume as measured by calculation from the dye plasma volume is indicated as RV; the red cell volume as measured directly with radioactive cells is indicated as R*V.

in the patient's blood after an hour are then determined. By the extent of the radioactivity dilution the cell volume of the recipient is calculated. The activity measurements are made on a Geiger counter, after digestion of the red cells to ferric hydroxide and electroplating this iron onto a copper planchette.

The application of this method to such a problem as this allows one to carry out two other types of observations. The first has to do with the relative survival

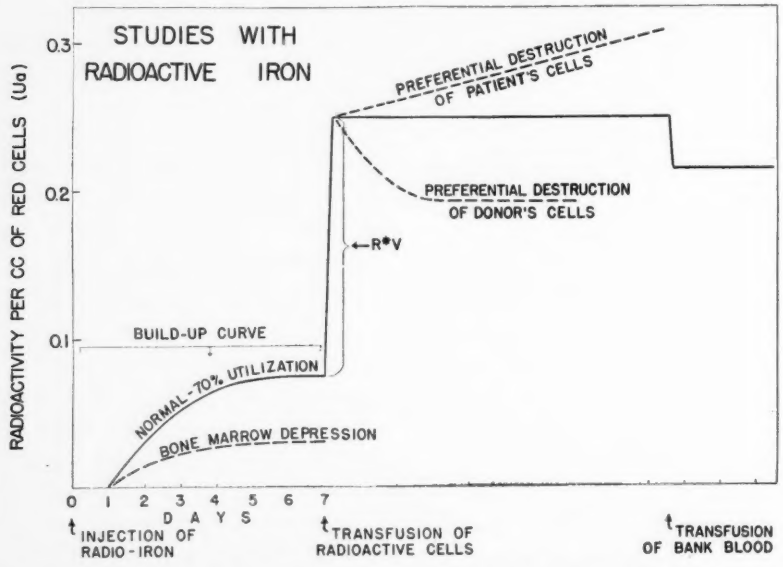


CHART 1.—Diagram demonstrating uses made of the radioactive isotopes of iron; the isotope Fe^{55} (five-year half-life) was employed.

Utilization of Radioiron: An injection of iron as ferric ammonium citrate given at zero-day results in a gradual appearance of the iron in the peripheral erythrocytes as shown in the solid line of "Normal—70% Utilization". An example of depression of this utilization is shown by the dotted line.

Measurement of Red Cell Mass: A transfusion of whole blood from a donor in whom erythrocyte hemoglobin has been synthesized from radioactive iron by multiple build-up injections, results in a sudden rise, the height of which is directly proportional to the red cell mass (R*V), and from this rise the R*V may be calculated.

Subsequent Fate of Cells: Following such a transfusion the concentration of radioactivity in the peripheral blood remains constant under normal conditions (solid line). Destruction of the donor's cells due to poor preservation or incompatability results in a drop in activity (lower dotted line). Active hematopoiesis also results in a fall of activity as ordinary iron is built into new cells.

If the patient's own cells are preferentially destroyed, a relative rise in activity (upper dotted line) would result.

Transfusions of ordinary bank blood result in a sharp fall in activity.

It should be emphasized that the radiation from this isotope of iron is a low energy *beta* ray which produces no known deleterious biologic effects in the small quantities used.

of the donor cells in the patient or the survival of the patient's own cells in his circulating blood. After a patient has received a radioactive transfusion, the radioactivity of his circulating cells will remain constant for long periods of time unless his cells and the donor cells are being destroyed in a differential fashion. For instance, if the patient is transfused with donor cells which have

been inadequately preserved or which are incompatible with the recipient, these cells will rapidly be destroyed and over a period of two or three days much of the radioactivity will disappear from the circulating blood as the radioiron is either excreted or stored again in the marrow for resynthesis. If the donor's cells are healthy, well-preserved erythrocytes, and the patient carries cells in his own blood which are either fragile or are being selectively destroyed at a rapid rate, then the specific radioactivity in the patient's circulating blood should gradually rise, as the patient's inactive cells are destroyed, and the donor's active

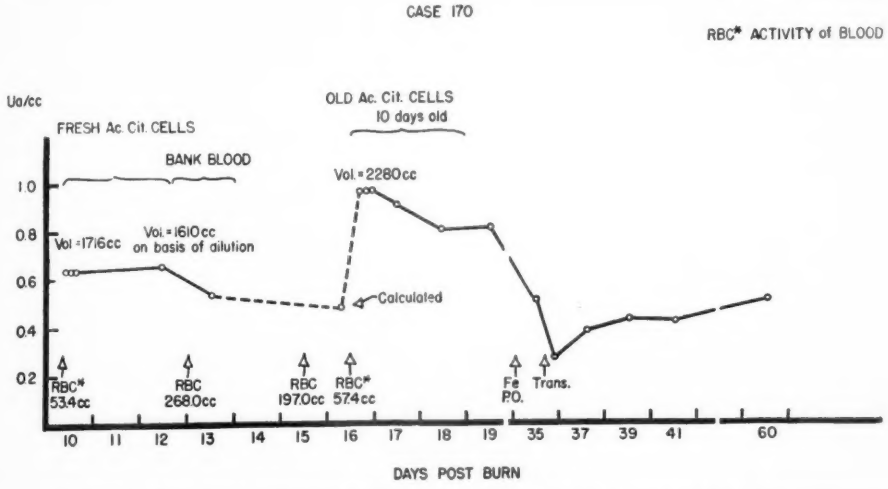


CHART 2.—Case 170: Radioactivity in peripheral blood in a patient with predominantly superficial burns, demonstrating dilution and preferential cell destruction phenomena of the radioactive iron technic diagrammatically represented in Chart 1.

On the tenth post-burn day the patient received 53.4 cc. of fresh, well-preserved radioactive cells yielding a calculated red cell mass (R*V) of 1,716 cc. (All figures in the chart are in cubic centimeters of cells.) On the 13th and 15th days transfusions of bank blood were given totalling 518 cc. of cells. On the 16th day a second radioactive transfusion was given increasing the concentration of cells containing radioactive iron in the peripheral blood. The second calculation of the red cell mass gave 2,280 cc., which figure indicates quantitative retention of the 518 cc. of cells given between the two measurements.

The second radioactive transfusion consisted of blood which had been poorly preserved (temperature inadequately controlled) and the fall in activity thereafter resulted from partial destruction of these fragile cells. Between the 19th and 35th day the patient's own marrow activity under iron therapy plus transfusions of bank blood resulted in a further fall, after which activity is essentially constant up to the 60th day.

cells remain viable. Therefore, over a period of days or weeks after the burn, determinations of the activity in a transfused patient permit one to draw conclusions as to whether or not the patient's own cells, which had been in the patient at the time of the trauma, are being selectively destroyed.

A second application of this technic involves a study of the build-up curves. If a normal individual is given a single intravenous dose of radioactive iron as ferric ammonium citrate, this iron will not appear in the circulating erythrocytes for about 24 hours as it is first taken up in the blood-forming organs and only slowly synthesized into hemoglobin. After this initial latent period the radio-

active iron begins to appear in the peripheral blood as erythrocyte hemoglobin at a characteristic rate and in a characteristic amount which may be described as an exponential rise in activity with a half-period of about three days and a final utilization of about 70 per cent of the injected radioactive iron. If, however, the patient is suffering from some disorder in which red cell formation is depressed, the appearance of this radioactive iron may either be slowed or its final utilization may be abnormally low. Conceivably, there may be situations in which bone marrow activity is increased and the build-up curve, therefore, either hastened or raised. We have not observed such patients, although we

TABLE II

Case 196
Male, Age 51, Weight 80 Kg.
Extent of Burn: 15 per cent total, 1 per cent third degree

RED CELL VOLUMES AND TRANSFUSIONS

Day Post-Burn	Red Cell Mass: Dye Method Cc. Cells	Red Cell Mass: Radioactive Method Cc. Cells	Transfusions Cc. Cells
0	2650		
3		2220	120
4		2470	97
9	3250	2350	114

PERIPHERAL BLOOD EXAMINATIONS

Day Post-Burn	R.B.C. Millions	Hemoglobin Gm./100 Cc.	Hematocrit % Cells	Reticulocytes %
0	4.44	18.5	44	
1			48	
2			47	
3			42	0.3
4				0.2
6	5.40	14.0		0.3
8	4.10			0.4
9	4.39		42	0.4
11	5.25			1.0
14	4.58			0.8
16	4.15			1.0

have not applied this technic to patients with such disorders as pernicious anemia in remission or true iron deficiency anemia under treatment. In Chart 1 some of the phenomena observable with radioiron are shown diagrammatically. In Chart 2 an example of such studies in a patient with a circumscribed burn is shown.

Operative blood loss has been computed from the concentration of acid hematin or of the radioactivity in the washings of sponges and drapes. The customary examinations of the circulating blood including reticulocyte counts have been carried out.

The end-products of red cell destruction have been measured in urine and feces because of our interest in the question of whether or not there was any correlation between the amounts excreted and the apparent destruction of red

cells in the blood. Both quantitative urobilinogen determinations[11] and the benzidine test have been carried out on urine and feces. On a few patients the hemoglobin concentration in the serum has been determined in the hours immediately following entry and the blood bilirubin concentration has been followed.

RESULTS

Data have been obtained from the study of four patients with predominantly second degree burns, and 13 patients with deep burns of considerable magnitude.

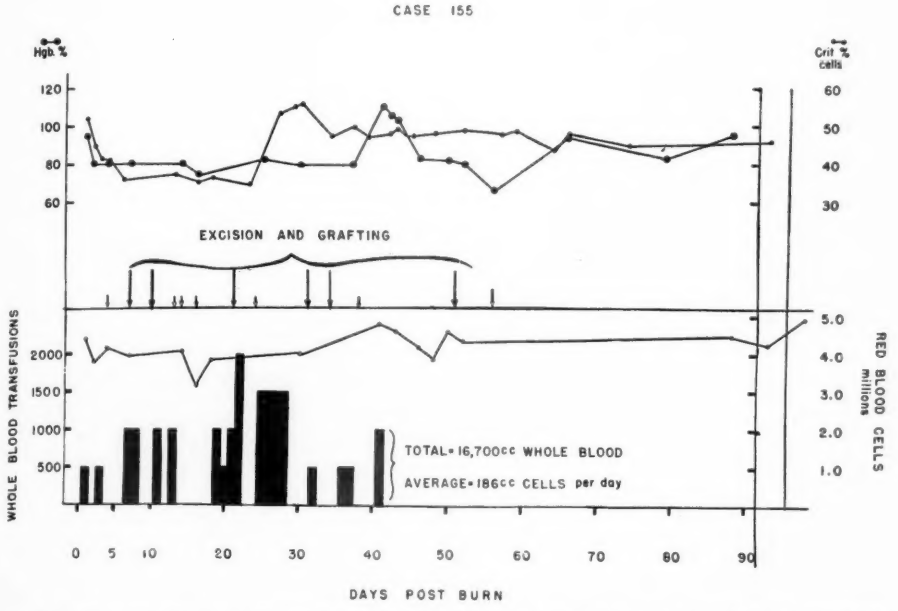


CHART 3.—Case 155: Peripheral blood findings and whole blood transfusions required by a patient with extensive deep burns (41 per cent total, 26 per cent third degree).

The whole blood given according to clinical indications succeeded in maintaining adequate peripheral red cell concentrations despite operations (large arrows) and dressings (small arrows). The amount given, therefore, approximated the requirements, and for the first 42 days averages 186 cc. of cells per day. These requirements included compensation for frank external loss at operation and dressing and for that reason cannot be compared with the red cell balances shown in Charts 5, 6, 7 and 8, which exclude such losses.

Of the latter, nine survived, and could be studied throughout their convalescence; four died of their injury.

1. SECOND DEGREE BURNS AND THIRD DEGREE BURNS OF LIMITED EXTENT

The four patients studied showed little tendency towards anemia. Viewed either from the point of view of peripheral cell concentrations, or red cell mass alterations, there is little significant evidence of red cell disappearance. An ex-

ample of the findings in one of these patients (Case 196) who showed no anemia is given in Table II.

One patient of this group (Case 254) had a total burn of 45 per cent and required energetic plasma therapy for the first 48 hours after his burn. The patient was group A. Studies of the two plasma pools used showed no anti-A antibodies in the first and an anti-A antibody titer of 1 : 64 in the second.* This patient alone of the second-degree group showed an increase in the excretion of

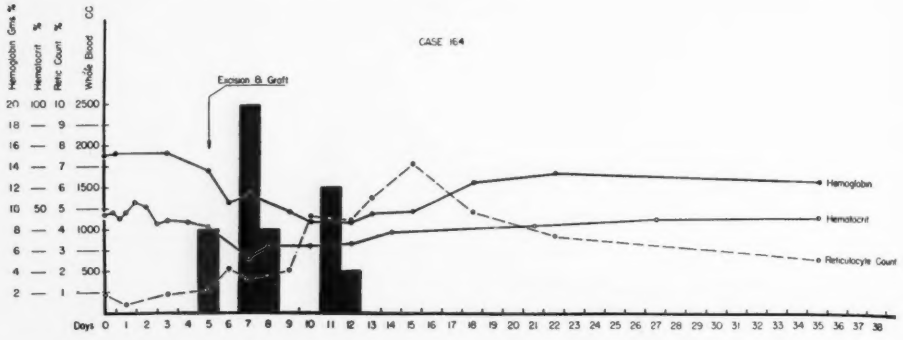


CHART 4.—Case 164: Hemoglobin concentration, hematocrit, reticulocyte response found and transfusions given a patient with moderately severe burns (36 per cent total, 7 per cent third degree).

An anemia became manifest on the sixth day and was not relieved until after the 22d day. Operation on the fifth day was attended by loss of blood presumably inadequately replaced by the 1,000 cc. of whole blood given (vertical black blocks). The red cell volumes (dye technic) were, on entry 2,510 cc., the second day 2,110 cc., and on the seventh day 1,210 cc. Accordingly, on the seventh and eighth days, respectively, 2,500 cc. and 1,000 cc. of blood was given. There was little effect on peripheral hemoglobin concentration and hematocrit but there was a rise in reticulocyte count. On the 11th and 12th days further transfusion again resulted in little immediate change in hematocrit or peripheral hemoglobin concentration but a further rise in reticulocyte count took place. Only after this regenerative response did the peripheral indices rise to normal. The red cell volume on the 27th day was 2,040 cc. These findings suggest (as do those in Case 269, Chart 9) that multiple closely spaced transfusions may be disappointing in their effects on red cell mass. They further indicate that transfusions do not suppress reticulocytosis in such a patient and that marrow regeneration may restore peripheral indices to normal quite rapidly.

urobilinogen in urine and feces during the second week following his burn. The low antibody (isohemagglutinin) titer probably precludes blood destruction from that source as the cause of this pigment excretion.

2. EXTENSIVE THIRD DEGREE BURNS

A. *Red Cell Mass (Dye) and Peripheral Blood Findings in Five Patients Surviving Injury:* These five patients are grouped together as the earlier patients studied before the isotope technic became available. Case 155 (Chart 3) demonstrates the amount of whole blood required to avoid anemia in an exten-

* We are indebted to Dr. Louis K. Diamond for these agglutinin studies which in this patient and in three others studied failed to demonstrate significant un-neutralized antibody titer in our plasma pools.

sive third degree burn patient subjected to early surgery. Case 164 (Chart 4) shows the disappointing effect of closely-timed red cell replacements. There is a subsequent rise to normal red cell count, but only after a striking reticulocyte response which was, in all likelihood, responsible for the return to normal. In Table III the total blood replacement required in these patients is shown.

All of these patients show red cell losses of 100-400 cc. per day during their early course; when one calculates the over-all red cell balance (*i.e.*, net volume change minus net replacement) this loss is apparent though its source, whether surgical or physiologic, is not clear. An example of such data is shown in Table IV. All figures in this table are in cubic centimeters of packed red cells; the

TABLE III

WHOLE BLOOD THERAPY IN PATIENTS WITH EXTENSIVE DEEP BURNS—EARLY SURGICAL CLOSURE

Case Number	Extent Burn Total/3°	Whole Blood Transfusions	Duration of Hospitalization
135	25/15	8,050 cc.	92 days
143	40/34	13,250 cc.	122 days
149	72/38	10,000 cc.	85 days
155	41/26	16,700 cc.	108 days
164	36/7	6,500 cc.	60 days

"loss per day" column indicates the average total loss per day (all sources) in the interval between the determinations. The magnitudes in this category are larger than those in subsequently described red cell balances because they include operative losses, whereas the balances are exclusive of such loss.

B. *Red Cell Mass, Radioiron Studies, Peripheral Blood Findings, and Pigment Excretion in Four Patients Surviving Injury:* The most extensive studies into the causes of the anemia encountered in deep burns were carried out in four patients who entered the hospital within the first hours after injury. All were treated with penicillin from entry. In three the life history of the burn was not disturbed by early operation; in one, excision of dead tissue was carried out on the eighth day after injury. The findings are recorded in detail in the form of case reports.

CASE 210

Case 210.—(Tables V and VI; Charts 5 and 6): A previously well, 34-year-old housewife, and mother of three, received a flame burn of 31 per cent of her total body surface, 25 per cent of her total surface being a third degree burn. Striking evidence of internal red cell destruction as well as excretion of the end-products of such destruction were demonstrated and the findings correlated well with a somewhat checkered clinical course. Although the patient made a good response to shock therapy, clinically, she seemed sicker during the first week than the extent of the injury would have indicated. On the eighth day an attempt was made to hasten the care of her deep burns and relieve her of the burden of wound infection, by excising the burns under general anesthesia. The wounds proved, in spite of the penicillin, to have developed a deep-seated inflammation and bled profusely on excision. Operation was stopped before half was excised, and none was grafted immediately as had

been planned. Because of the poor clinical reaction to operation, grafting even of the excised area was not started until the twenty-first day. At this time the excised wounds were coated with fiery, infected granulations, while the unexcised were edematous, with evidence of deeper infection. Her later course was one of repeated skin graftings, slow healing, with gradual clinical improvement, and discharge about four months after entry.

Early Hemolysis: On the day of admission the patient showed evidence of nemolysis. A hemoglobin concentration of 0.11 Gm./100 cc. in the serum was observed in the first three hours after injury. Such a high level of free hemo-

TABLE IV

RED CELL VOLUMES, TRANSFUSIONS, AND AVERAGE LOSSES PER DAY (IN CUBIC CENTIMETERS OF CELLS)

Case 143 Male, Age 17, Weight 58.7 Kg. Extent of Burn: Total/40% 3°/34%				Case 149 Male, Age 20, Weight 66.1 Kg. Extent of Burn: Total/72%3°/38%				Case 164 Male, Age 32, Weight 71.2 Kg. Extent of Burn: Total/36% 3°/7%			
Day	Red Cell Mass (Dye)	Transfusions	Losses Per Day	Day	Red Cell Mass (Dye)	Transfusions	Losses Per Day	Day	Red Cell Mass (Dye)	Transfusions	Losses Per Day
2	2,130			0	2,750			0	2,510		
6	1,650	420	185	2	1,920		400	2	2,110	420	410
40	1,600	4,750	140	6	2,350	840	120	7	1,210	1,125	400
65	1,890	1,125	34	42	2,380	3,260	90	27	2,040	1,125	15
				85	2,220						

PERIPHERAL BLOOD FINDINGS

Day	R.B.C. Millions	Hb. Gm.	Hematocrit % Cells	Day	R.B.C. Millions	Hb. Gm.	Hematocrit % Cells	Day	R.B.C. Millions	Hb. Gm.	Hematocrit % Cells
0	6.45		55	0			70	0	5.60	18.4	47
2	5.40		47	1			57	1	4.90	17.6	49
3	5.07		44	2			50	3	4.50	15.1	44
5	3.82	14.4	42	4	5.00	12.8	30	7	3.00	11.0	28
7	5.53	14.2	40	6	5.60	11.2	42	13	3.80	9.4	39
10	3.60	9.6	37	9	3.80	11.2	35	18	3.80	12.5	42
16	3.53	14.4	49	13	4.38	11.2	39	35	5.10	12.5	46
27	3.53	9.6		25	4.20	12.8		42			45
34	4.34	13.6	40	42	4.40	13.0	48	51			50
45	4.54	14.4	45	52	4.20	12.8	45				
75	4.80	14.4	48	85			49				
103	4.64	15.5	54								

globin in the serum points to a comparatively large initial destruction of red cells. Only one patient of our series showed a greater concentration, 0.17 Gm./100 cc. in Case 234. The volume of red cells destroyed cannot be computed accurately from the concentration of free hemoglobin in the serum.*

* Hemoglobin injected into the blood stream as free hemoglobin[12] is rapidly removed and it is impossible from the serum value to calculate the total amount released by hemolysis if the hemolysis continues over a period of hours. If the serum concentration is multiplied by the plasma volume, it yields a figure of only 1.9 Gm. of hemoglobin, an obviously low figure. It would probably be more accurate to multiply the concentration by the volume of the entire extracellular space because hemoglobin, being a protein of low molecular weight (68,000), probably equilibrates into the extracellular space even more rapidly than albumin. Its rapid removal by the spleen, marrow, liver and kidney, makes any such calculation but an estimate.

Internal Red Cell Disappearance: The red cell balance, based on periodic measurements of the red cell mass, the addition of all cells lost by sampling and at operation and the subtraction of all given by transfusion, showed an early rapid and later slow disappearance of red cells from the circulation (Table V and Chart 5).

Reference to Table V shows, first, that the dye method for the measurement of the red cell mass checks well with the radioactive technic except in the early phase immediately following the burn. In this phase the presence of abnormal

TABLE V

Case 210

Female, Age 34, Weight 73 Kg.

Extent of Burn: 31 per cent total, 25 per cent third degree

RED CELL BALANCE

Period	Days After Injury	Red Cell Mass		Red Cell Accounts			Red Cell Balance Change Per Day	
		Dye Method	Radioactive Method	Transfusions Given	Samples Taken	Op. + Dressing Losses	Dye Method	Radioactive Method
I	0— 5	2010—(880)	1535—1370	263	68	0		— 90
II	5— 8	(880)—2100	1370—2100	756	18	0		— 3
III	8— 15	2100—2590	2100—2110	2118	39	730	—122	—191
IV & V	15— 34	2590—1560	2110—1410	1600	87	813	— 91	— 74
VI	34— 49	1560—1660	1410—1440	185	52	250	+ 16	+ 11
VII	49— 64	1660—2150	1440—1820	486	28	450	+ 32	+ 25
VIII	64— 86	2150—1860	1820—1720	52	25	68	— 11	— 3
IX	86—114	1860—1850	1720—1440	0	0	0	0	— 10
X	114—127	1850—2130	1440—(800)	0	0	0	+ 22	

(All figures are in cubic centimeters of packed red cells.)

RADIOIRON UTILIZATION

Period	Days After Injury	Radioiron Utilization Per Cent	Per Cent of Normal Utilization
V	28— 34	45.0	65.0
IX	93—102	47.2	68.0

capillary permeability in the wound and hemoglobin or other pigments in the serum may render the dye determination untrustworthy. The table shows, second, under "Red Cell Accounts," the enormous volumes of blood which may be lost by operative excision of a wound eight days after injury from granulating wounds into dressings and in grafting. The figure of 730 cc. in Period III under "Operation and Dressing Losses" represents 1,750 cc. of whole blood lost during the excision of slough. The subsequent figures show how large in aggregate may be the continued small loss into dressings and from grafting. A loss of 75 to 150 cc. of whole blood was determined each time the dressings were changed and a loss up to 200 cc. with each grafting.

The third section of Table V, "Red Cell Balance," details the average loss, or gain, of red cells per day after proper adjustment has been made for transfusions, sampling and dressing and operation loss. In the first five days,

Period I, there was an average disappearance of 90 cc. of red cells per day. From the fifth to eighth days, Period II, an approximate balance was achieved. Immediately following the wound excision, which took place between Periods II and III, there was a severe loss of circulating red cells which lasted through Period V. For the week of Period III approximately 200 cc. of red cells disappeared each day, while in the subsequent 19 days of Periods IV and V an average of 75 cc. per day could not be accounted for. It would appear that the

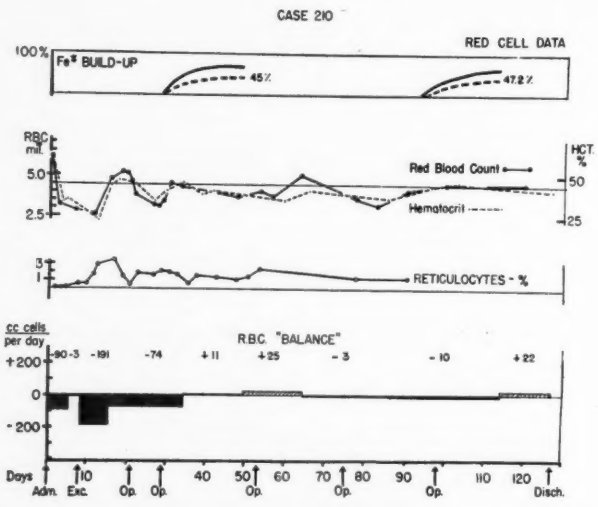


CHART 5.—Case 210: Radioiron utilization, peripheral blood findings and red cell balance demonstrating early progressive red cell destruction in a severely burned patient (31 per cent total, 25 per cent third degree).

The radioiron utilization curves (Fe* build-up) are diagrammatically shown. The solid line indicates the normal curve of 70 per cent utilization. The dotted lines indicate the observed values and on both occasions demonstrate some bone marrow depression due either to iron deviation or toxic depression of the bone marrow.

Red cell counts, hematocrit and reticulocyte counts show an early profound anemia followed by a reticulocyte rise, and later, maintenance of nearly normal peripheral indices.

The red cell balance (cf. Table V) is an expression of the net red cell formation or destruction as elucidated by serial measurements of the red cell mass. In this patient an early destruction is followed by a period of little change (average destruction of 3 cc. of cells per day) and then a secondary red cell destruction correlated in appearance with a partial excision of the burn wound.

Subsequent to the 35th day, destruction and formation are equally balanced, and there is less significant net change in red cell mass.

operative procedure, whether by a nonspecific incitation of metabolic changes or by kindling the infection, had tipped off this renewed internal or hidden red cell destruction which lasted three and a half weeks.

Throughout the second month after injury, Periods VI and VII, this patient achieved a positive balance of red cells; that is, she was able to make more than she was destroying internally. At the beginning of the second month, however, there was again evidence of internal red cell disappearance with a slight negative balance lasting for seven weeks, Periods VIII and IX.

Peripheral Blood Correlation: The examination of the peripheral blood by red blood cell count, hematocrit and hemoglobin concentration (Table VI and Chart 5) revealed for the greater portion of the period of hospitalization a close correlation between the red cell mass and the anemia in the peripheral blood. Only from the second to eighth day, when there was evidence of an enlarged plasma volume, did the peripheral anemia exceed the observed fall in red cell mass; such an anemia is, therefore, termed false. Two and a half months after entry the patient again developed a peripheral anemia, at the time when her red

TABLE VI

Case 210
Female, Age 34, Weight 73 Kg.
Extent of Burn: 31 per cent total, 25 per cent third degree

SERUM HEMOGLOBIN

Day + Hour Post-Burn	Hemoglobin Gm./100 Cc. Serum
0+2.5	0.11
0+3	0.11
0+4	0.10
0+4.5	0.06
0+7.5	0.02

PERIPHERAL BLOOD EXAMINATIONS

Day Post-Burn	R.B.C. Millions	Hemoglobin Gm./100 Cc.	Hematocrit % Cells	Reticulocytes %
0	6.04	17.7	58	
1		16.3	51	
2	3.25	13.5	44	
3			35	
4			37	
5			34	
6	2.91	12.0	36	0.6
11	2.64	8.0	25	1.7
15	4.80	16.8	44	3.5
21	3.85	14.0	44	2.0
26	3.26	13.5	34	1.2
34	4.30	17.0	42	0.8
42		15.0	41	1.5
50	4.95	14.0	35	1.6
53	4.08	14.3		2.7
56	2.82	12.0	35	
63	5.06	14.5	41	
77	3.70	13.0		1.5
82	3.20	13.8		
93	4.15	12.5	41	1.5
114			39	
127			40	

cell balance reverted to slight negativity. This anemia was repaired coincident with complete healing.

Excretion Products of Red Cell Destruction: Studies of the excretion of the end-products of red cell destruction in this patient (Chart 6) were illuminating as they corroborated in a satisfactory way the measurements already described of the patient's circulating red cell mass. During the first two weeks the patient was in the hospital, she showed consistently positive benzidine test in the feces, indicating that some hemoglobin or heme was being excreted intact

into the gastro-intestinal tract either through the biliary apparatus or through the large bowel mucosa. This is a constant finding in burn patients and has previously been reported,[13] but this patient demonstrated the phenomenon to an unusual degree and for a protracted period. The urine urobilinogen excretion is somewhat elevated on the first observation and then on the tenth day, shortly after the period of zero red cell balance the urine urobilinogen returned to normal.

Radioiron Utilization: During the course of the patient's convalescence, starting on the twenty-eighth day and again on the ninety-third day, two radio-

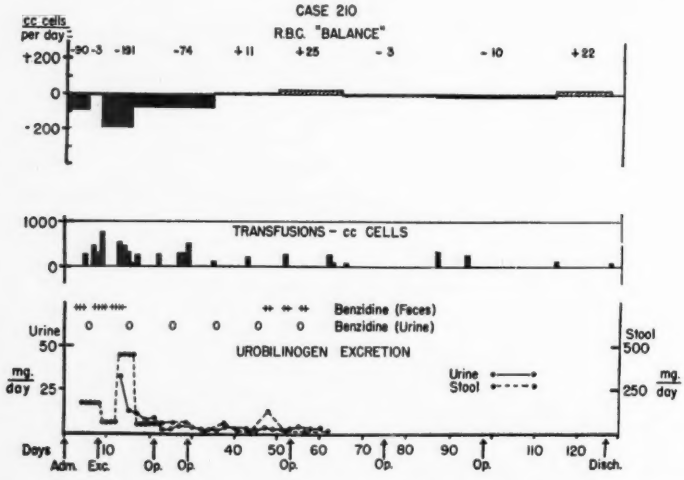


CHART 6.—Case 210: Red cell balance, transfusions and pigment excretion in the same severely burned patient as in Chart 5.

The red cell balance is repeated for orientation. The transfusions, recorded in cubic centimeters of cells, were administered according to clinical indications. It is apparent that their timing follows each of the first two periods of red cell destruction indicated by negative red cell balances.

The urobilinogen excretions are shown in milligrams per day in urine and stools. There is an increased excretion of this end-product of hemoglobin metabolism up to the 15th day, after which it is essentially normal.

Benzidine-reacting material is present in feces in the early period of destruction; the urine benzidine is consistently negative.

iron build-up curves were carried out, both of which showed some depression of bone marrow activity. The first curve showed 45 per cent utilization of the radioiron, which is only about 65 per cent of normal, and the second build-up curve showed 47.2 per cent utilization of the iron which is about 67.5 per cent of normal. As the result of these tests of marrow function a part of the anemia tendency late in the convalescence of this patient may be interpreted as due to inadequate bone marrow response. This, in turn, may be due to one of two factors, either inadequate supply to the marrow of hemoglobin precursors, especially iron, or secondly, alteration in bone marrow function as a result of the presence of a large, infected open wound. The iron utilization curves do not indicate which mechanism was operating.

Reticulocyte Response: During the maximal period of red cell destruction of the secondary anemia phase, the patient's reticulocyte response rises to 3 per cent in the peripheral blood and is maintained near 1 per cent for approximately two months, indicating little marrow activity as shown also by the poor radioiron utilization.

Summary and Discussion: This patient showed every laboratory and clinical evidence of massive internal red cell destruction. Many transfusions were required to maintain peripheral red cell concentrations within the normal range. There was slight evidence of bone marrow response, as indicated by the reticulocyte count, but this bone marrow response was probably subnormal, as indicated by the impaired utilization of radioactive iron.

TABLE VII

Case 217
Female, Age 26, Weight 92.8 Kg.
Extent of Burn: 78 per cent total, 45 per cent third degree

RED CELL BALANCE

Period	Days Post-Burn	Red Cell Mass: Dye Method	Red Cell Mass: Radioactive Method	Red Cell Accounts: Transfusions Given	Red Cell Accounts: Samples Taken	Red Cell Accounts: Op. + Dressing Losses	Red Cell Balance Change Per Day: Dye Method	Red Cell Balance Change Per Day: Radioactive Method
I	0— 3	2320—1410	—1380	742	59	0	—318	
II	3—11	1410—1690	1380—1250	45	63	0	+ 50	—19
III	11—16	1690—	1250—1930	742	43	135		+23
IV	16—25	—2160	1930—1830	101	10	0	— 14	—21
V	25—49	2160—2200	1830—2150	1850	85	531	— 50	—38
VI	49—71	2200—2160	2150—2010	1470	25	157	— 60	—65
VII	71—98	2160—(1660)	2010—2240	97	59	202		+15

(All figures are in cubic centimeters of packed red cells.)

RADIOIRON UTILIZATION

Period	Post-Burn	Radioiron Utilization Per Cent	Per Cent of Normal Utilization
I	0— 5	15.0	21.0
V	31—36	59.0	84.0
VII	80—85	70.0	100.0

It is difficult to know what rôle the operative procedure on the eighth day played in this anemia which became so much intensified after the operation. It should be emphasized again that the figures for red cell balance are over and above the operative and dressing losses and that, therefore, the increase in anemia tendency after the operation must be related either to continued insensible red cell loss into the wound or to some alteration in metabolism, possibly related to the alarm reaction following the operation. In any event, it is apparent that this patient needed one whole blood transfusion every three days in the first week and an average of one every two days in the next three weeks in order to maintain a constant red cell mass, entirely apart from the blood needed to replace operative and dressing losses.

CASE 217

Case 217.—(Tables VII and VIII; Charts 7 and 8): While tending a coal stove, the clothes of a robust, well-nourished single woman, age 26, caught on fire; 78 per cent of her body surface was burned, 45 per cent of the total body surface being of full-thickness destruction. Shock was successfully prevented with massive doses of plasma intravenously and an equivalent volume of oral fluids. During the phase of gradual resorption of the edema from the interstitial space, her kidneys were able to keep pace by a huge volume output and she had, therefore, only moderate and nonincapacitating hemodilution. Penicillin, in large doses, was started at entry and it was planned to start the excision and grafting of

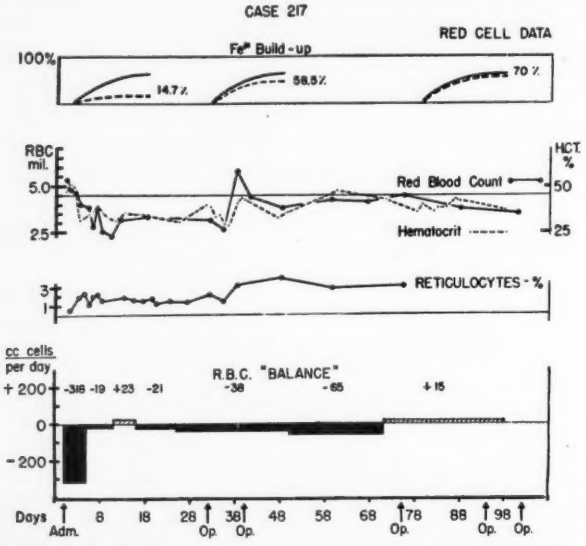


CHART 7.—Case 217: Radioiron utilization, peripheral blood findings and red cell balance demonstrating an early and late progressive anemia in an extensively and deeply burned patient (78 per cent total, 45 per cent third degree).

The radioiron utilization (Fe* build-up) is shown diagrammatically as in Chart 5 (Case 210). The first test done on entry showed little elaboration into peripheral erythrocytes, correlating with the relative lack of reticulocyte response; about the 30th day marrow function had improved, evidenced by better iron utilization as well as increase of reticulocytes to 4 per cent. By the 85th day utilization was normal.

The peripheral counts demonstrate an early profound anemia with relatively little reticulocyte response, followed about the 35th day by a rise with reticulocyte increase coincident with massive transfusion. Thereafter, nearly normal levels were maintained.

The red cell balance is shown as in Chart 5 (Case 210). There is an early massive red cell loss (internal destruction) followed by relative balance until about the 50th day when, for about three weeks, cell disappearance increased again. After this period a slightly positive balance obtained.

the full-thickness wounds on the seventh day. Fever appeared early, however, and had risen to 103° F. by the day before the intended operation. Widespread, moderately invasive infection beneath the deep burns (despite penicillin) was evident at change of the dressings and plans for early operative closure were abandoned. Grafting was eventually accomplished on the granulating base left after spontaneous separation of the slough. The first grafting was done on the fortieth day. The course of this patient was, therefore, less trammeled by operations than Case 210 and the anemia is more characteristic of that which is to be expected as the consequences of the burn alone.

Early Hemolysis: On the day of her burn the patient showed free hemoglobin in the serum to the extent of 0.12 Gm./100 cc., evidence of early red cell destruction.

Internal Red Cell Disappearance: The data on red cell volumes in this patient are shown in Table VII. A radioactive red cell volume was not determined on admission because it was decided instead to carry out an early build-up curve. However, in the patient's first five days, there is a marked destruction of red cells as indicated by the dye method, and as will be seen below this was correlated with urobilinogen excretion and doubtless represents the true situation.

After this initial destruction, the patient goes into a much less spectacular secondary phase than was the case with the previous patient. There is a de-

TABLE VIII

Case 217
Female, Age 26, Weight 92.8 Kg.
Extent of Burn: 78 per cent total, 45 per cent third degree

SERUM HEMOGLOBIN

Day + Hour Post-Burn	Hemoglobin Gm./100 Cc. Serum.
0 + 1	0.12
0 + 1.5	0.10
0 + 2.5	0.10

PERIPHERAL BLOOD EXAMINATIONS

Day Post-Burn	R.B.C. Millions	Hemoglobin Gm./100 Cc.	Hematocrit % Cells	Reticulocytes
0	5.30	16.0	43	
1	4.90	18.0	39	1.2
2	4.80	13.6	47	0.0
3	4.00	10.4	33	2.1
4	2.90	12.8		2.5
5	3.91	13.0	35	1.1
8	3.00	10.0	35	1.9
15		13.5		1.8
24		12.5		1.3
32	3.26	11.7	40	2.2
48	3.83	11.5	34	4.0
67	4.20	14.2		
88	3.87	12.0		0.3
101	3.51	9.8		
123	4.35	14.5		
179	4.50	14.4		

struction of red cells varying from 20 to 60 cc. a day for the next two months before the patient finally achieves a positive red cell balance.

Peripheral Blood Correlation: The determinations of the degree of anemia in the peripheral blood (Table VIII, and Chart 7) in this as in the previous patient followed closely the observed red cell mass except during the phase of hemodilution. This phase, or period of false anemia, was encountered from the second through approximately the eleventh day.

Excretion Products of Red Cell Destruction: The data of the excretion of the products of red cell destruction are shown in Chart 8. The excretion of urobilinogen in the urine is initially normal. The subsequently elevated values overlap the periods of red cell destruction. It appears both from the onset and the downward slope of the initial curve that there is a latent period (about 48 hours) between the release of hemoglobin in the circulation and the appearance of

unusual amounts in the urine as urobilinogen. Then from the eighth to sixteenth hospital day, shortly after the period when the patient was in transient zero balance, the urine-urobilinogen was normal. From the eighteenth to the sixtieth hospital day there were intermittent rises in urine-urobilinogen when the patient was destroying 20 to 60 cc. of cells per day. On the twentieth day a cystitis was recognized. There was no rise in excretion following the first grafting on the fortieth day but there was a peak the day

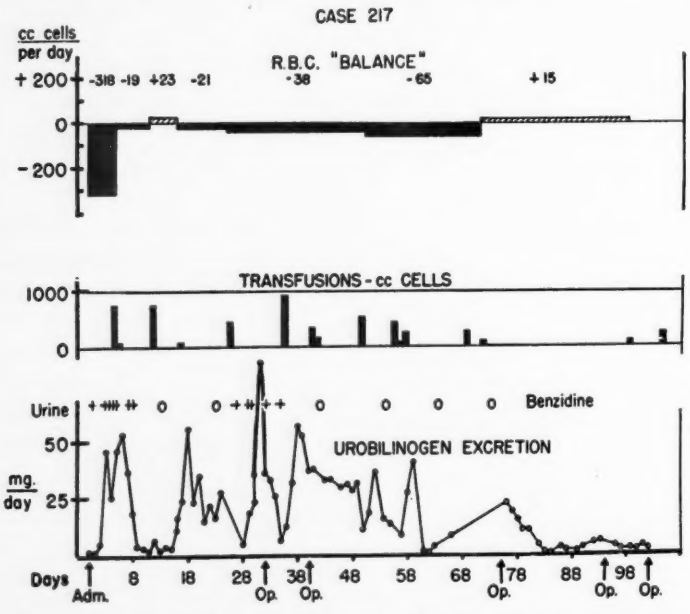


CHART 8.—Case 217: Red cell balance, transfusions and pigment excretion in the same severely burned patient as in Chart 7.

The red cell balance is repeated for orientation.

Transfusions (recorded in cubic centimeters of cells) were administered according to clinical necessity, and in this case there was no external loss from early operative excision.

Pigment excretion in the urine shows a striking rise, starting four days after entry, presumably in response to the early internal destruction shown by the negative balance. Excretion returns to normal on the ninth day only to rise again and remain elevated with occasional peaks until the 85th day, when, with slightly positive red cell balance internal destruction has evidently ceased.

Benzidine-reacting material is excreted in the urine coincident with the urobilinogen peaks.

following grafting of the back on the seventy-fifth day. After the eightieth hospital day the urine excretion figures remain in the normal range despite further surgery.

The urine shows a positive benzidine test during the high peaks of urobilinogen excretion indicating that either heme or hemoglobin is being excreted in the urine along with the metabolic end-product, urobilinogen.

Radioiron Utilization: The regenerative activity of the bone marrow was tested during three stages of the patient's convalescence. Radioiron was injected intravenously the day of entry and its elaboration into circulating red cells was

observed during the succeeding six days (Table VII and Chart 7). (In order to make this measurement, no radioactive transfusions were given during these days.) Only 21 per cent of the expected activity appeared in the circulation, indicating a severely depressed activity of the marrow. The second injection of radioiron was made on the thirty-first day. The marrow was more active than before but still somewhat depressed, the elaboration of the iron being 84 per cent of the expected normal. Such marrow synthesis is interesting in view of the extensive areas of open infected wounds. Six weeks later, two and a half months after entry, activity of the bone marrow was normal as judged by the third injection of radioiron.

Reticulocyte Response: The rise in bone marrow function as indicated by the second injection of radioiron was accompanied by a reticulocyte response from 2 to 3 per cent, and later 4 per cent (Chart 7).

Summary and Discussion.—As did the previous patient, this extensively and deeply burned patient showed evidence of massive internal destruction of red cells. Also, like the previous patient, she passed through a prolonged period of disordered physiology, with high fever, water retention and severe clinical illness. Both patients developed large open wounds.

Both showed an early acute red cell destruction of 100 to 300 cc. per day and lasting about four days. This phenomenon is interpreted as being the destruction of red cells whose viability had probably been altered by exposure to heat while circulating in the burned area at the time of the burn, though we have no proof of the veracity of this interpretation.

After this initial destruction, both patients show a transient period of essentially zero red cell balance followed by a secondary phase of red cell destruction not as spectacular as the early loss. In the first patient this secondary phase is quite acute, apparently related to the operative procedure carried out at that time. No such operation was carried out in this second patient and her later curve is smoother. Both patients showed late destruction far on into their convalescence which is correlated with occasional relapses of their anemia. An increased urobilinogen excretion corroborated the data derived from the volume measurements. Evidence of bone marrow suppression was found in both patients as subnormal levels of iron utilization. The reticulocyte counts correlated with the observed changes in iron elaboration but did not give indication in themselves, therefore, of the degree of deficiency of the red cell mass.

Case 260

Case 260.—While celebrating her impending departure for a tuberculosis sanitarium, the clothes of a 27-year-old, childless housewife, caught on fire, burning 28 per cent of her body surface, 12 per cent of her total surface showing full-thickness destruction. In anticipation of her developing a progressive anemia it was planned at entry to follow the erythrocyte changes and postpone all possible influences, such as transfusion and early operation, until the nature of the anemia was established. Her red cell mass was immediately measured with radioactive red cells. Her wounds were dressed without débridement or cleansing, and she was started on penicillin. The first grafts were placed on freshly excised wounds on the ninth day. The remaining areas were grafted at approximately weekly intervals, and the patient was discharged at the end of three months.

To our surprise she developed no true anemia. It was also true that she never developed a negative nitrogen balance. Both of these findings may be attributed to the relative absence of invasive infection and to a continuously good appetite.

From the third to the fifth days a mild anemia was observed in the peripheral blood. This was interpreted as a false anemia since the red cell mass (by radioactive technic) at entry was 1,475 cc., and seven days later 1,490 cc. Between these virtually identical determinations, 138 cc. of cells had been removed in sampling and no transfusion had been given. Though no significant alteration in the red cell mass was observed, there is evidence of excretion of the end-products of red cell destruction in supernormal quantities. From her fifth to

TABLE IX

Case 269
Male, Age 60, Weight 89 Kg.
Extent of Burns: 27 per cent total, 20 per cent third degree

PERIPHERAL BLOOD EXAMINATIONS

Day Post-Burn	R.B.C. Millions	Hemoglobin Gm./100 Cc.	Hematocrit % Cells	Reticulocytes %
1	5.63		59	1.1
2	5.09		47	1.4
4	4.09		40	1.1
6	4.68		39	1.0
8	4.20	11.2	35	1.0
10	3.20		37	
20	3.50		34	1:0
30	3.90		39	
47	3.95	11.5	38	0.5
68	4.00	9.5		1.0

tenth days the patient excreted, intermittently, slightly increased amounts of urobilinogen, the first peak being on the fifth and sixth days and the second peak following immediately her excision and grafting on the ninth day. Associated with this evidence is the presence of weakly positive benzidine-reacting material in the urine from the second to the seventh days, the period during which, it will be recalled, she showed a transient peripheral anemia. It is also of interest that during the latter phase of this period, the patient showed a definite reticulocyte response, suggesting that from the tenth day forward, her bone marrow could compensate for any red cell destruction.

CASE 269

Case 269.—(Tables IX, X and XI; Chart 9): This patient, age 60, apparently drunk when trying to fill a kerosene stove, was burned when his oil-soaked trousers ignited. Burned around the legs and lower trunk, he crawled into bed and was seen first by a doctor the next day. Twenty hours after injury he reached the hospital, showing extensive deep burns of the legs, buttocks, scrotum and perineum. It was estimated that 27 per cent of the body surface was burned, three-quarters of the burns being full-thickness.

Whole blood-transfusions and early operation were purposely withheld in order to learn the character of the anticipated anemia. The patient was given penicillin intramuscularly. The burn slough was allowed to separate spontaneously and the first grafts were

applied on the thirty-sixth day. Subsequent graftings were accomplished periodically. The patient was discharged on the one hundred and twenty-sixth day.

Early Hemolysis: There was no elevation of serum hemoglobin on admission to the hospital.

Internal Red Cell Disappearance: The circulating red cell mass was measured by the radioactive technic four times during the patient's convalescence.

TABLE X

Case 269
Male, Age 60, Weight 89 Kg.
Extent of Burn: 27 per cent total, 20 per cent third degree

URINARY EXCRETION OF BILE PIGMENT

Day Post-Burn	Urobilinogen Mg./24 Hr.	Benzidine
0	0.0	
1	13.6	—
2	8.2	±
3	6.2	±
4	17.4	±
5	23.9	—
6	13.4	—
7	7.4	—
8	5.8	—
9	14.8	—
10	14.0	—
11	17.3	—
12	8.3	—
13	9.5	—
14	8.2	—
15	8.7	—
16	8.7	—
17	6.6	—
18	10.8	—
19	6.1	—
20	4.2	—

TABLE XI

Case 269
Male Age 60, Weight 89 Kg.
Extent of Burn: 27 per cent total, 20 per cent third degree

RED CELL BALANCE

Period	Day Post-Burn	Red Cell Mass (Radioactive)	Transfusions	Samples Taken	Red Cell Balance
I	0–12	2780–1773	0	150	−72
II	12–25	1773–2077	147	40	+15
III	25–34	2077–2564	1311	150	−85

(All figures are in cubic centimeters of packed red cells).

The measurements were made on the day of entry, the twelfth, twenty-fifth and thirty-fourth days. During the first 12 days, between the initial and second volume studies, there was a disappearance of 857 cc. of red cells, or 72 cc. of cells per day. The disappearance of these cells was shared in equal proportion by the patient's cells and those from the radioactive donor. Since the latter were not in the body at the time of the injury, this disappearance presumably was not the direct result of heat on cells.

During the second period, between the second and third red cell volume determinations, the patient showed a net red cell gain averaging 15 cc. of cells per day, and the concentration of radioactivity of his circulating cells slowly decreased as further evidence of regeneration. In the third period, between

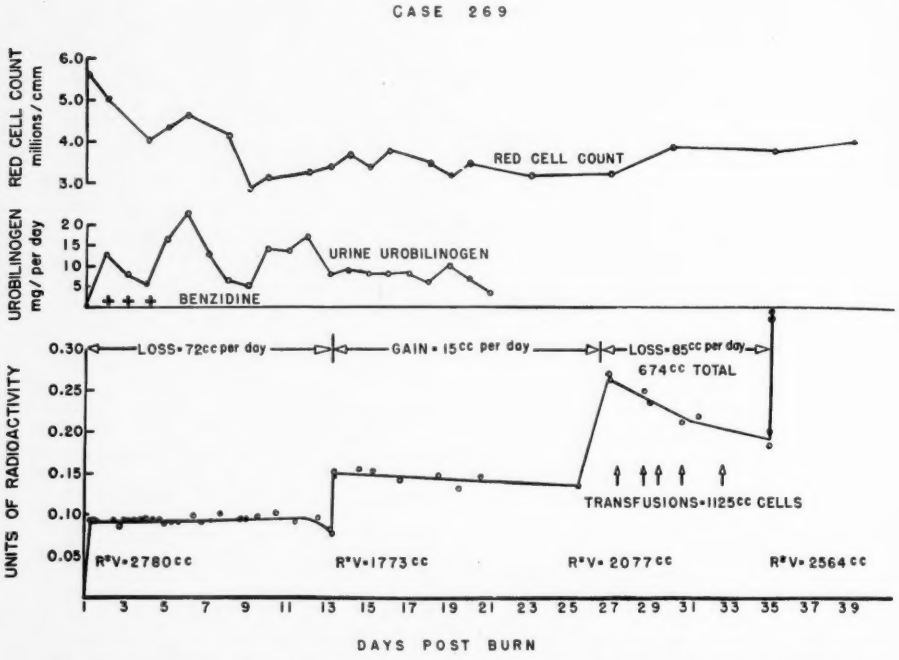


CHART 9.—Case 269: Red cell counts, urobilinogen excretion and radioiron data showing an early progressive anemia in a severely burned patient (27 per cent total, 20 per cent third degree).

Whole blood transfusions were withheld until the 27th day post-burn except as necessary to measure the red cell mass (R*V). To such purpose, radioactive transfusions were given on the first, 13th, 26th and 35th days. A peripheral anemia developed in the first ten day with a falling red count, evidence of increased urobilinogen excretion and a loss of 72 cc. of cells per day (average) during the first two weeks. During this time the radioactivity of the patient's red blood cells (resulting from an active transfusion the first day) did not alter significantly, indicating that his own cells and those of the radioactive donor partook equally of the destruction.

From the 13th to 26th day the red cell count remained stationary, urobilinogen excretion was not elevated, and the patient showed an over-all gain of 15 cc. of cells per day (average); the peripheral radioactivity fell slightly, indicating active regeneration sufficient to prevent further anemia but not sufficient to compensate entirely for previous cell losses.

Starting on the 27th day the patient was given five transfusions totalling 1,125 cc. of cells. The red count rose very little and the red cell mass increased only 500 cc. (The drop in radioactivity was due to dilution of the active cells by bank blood, cf. Chart 1.) The findings suggest that multiple closely spaced transfusions may give disappointing results in terms of red cell mass changes.

his third and fourth cell volume determination, the patient was given five whole blood transfusions, totalling 1,125 cc. of cells, as well as the small amount of radioactive cells given him, but the total increment in volume was only about 500 cc. The calculated destruction of cells during this period is 674 cc. The

period involved is eight days long and the cell destruction per day, therefore, averaged 85 cc.

The reason for this massive disappearance of red cells and failure to rebuild completely the red cell mass is not clear. The downward slope of the curve of concentration of radioactivity in this last period of observation is what should be expected from the increase in size of the red cell mass, the radioactive cells remaining in the circulation. Whether the entire disappearance was at the expense of the recently transfused cells cannot be determined from the findings. The patient showed no untoward clinical reaction to his transfusions.

Excretion Products of Red Cell Destruction: The disappearance of red cells in the initial period was accompanied by a rising excretion of urobilinogen which reached a peak on the fifth day after injury of 23.9 mg. Following this

TABLE XII

Case 234
Male, Age 68, Weight 60 Kg.
Extent of Burn: 55 per cent total, 45 per cent third degree

RED CELL VOLUMES, TRANSFUSIONS, AND RED CELL BALANCE

Day Post-Burn	Red Cell Mass (Radioactive)	Transfusions	Samples Taken	Red Cell Balance
0	2030			
3	1600	75	59	148
7	1420	300	76.5	100

(All figures are in cubic centimeters of packed red cells.)

Day + Hour Post-Burn	Serum Hemoglobin Gm./100 Cc.
0 + 8	0.16*

* Earlier serum hemoglobin estimations showed larger amounts of hemoglobin to be present, but a quantitative result was not obtained because of the inaccuracy of the colorimeter in dealing with high hemoglobin concentrations in undiluted serum.

peak there was a gradual decline during the 20 days the measurements were made. There was but a transient and early excretion of benzidine-positive material in the urine.

Summary and Discussion: This patient showed two periods of red cell destruction with a period of red cell regeneration and increase in red cell mass between. The early period of destruction and the relative constancy of red cell radioactivity constitutes evidence that in this patient, at least, the anemia was not due to selective destruction of the patient's own cells on the basis, for instance, of heat sensitization or fragility. It suggests that the red cell destruction included proportionately both the patient's own (burned) cells and those (unburned) infused from the radioactive donor.

The later period of destruction demonstrates the occasional costliness of repeated transfusions. More than half of the volume of cells given in five transfusions disappeared during the eight days during which they were administered.

C. *Red Cell Mass, Radioiron Studies, Peripheral Blood Findings and Pigment Excretion in Four Patients Not Surviving Injury:* The four extensively and deeply burned patients of this group are of considerable interest due to variations from the preceding group of surviving patients.

Case 234.—(Table XII): An elderly man showed all the phenomena we have come to associate with the burn anemia—hemoglobinemia, hemoglobinuria,

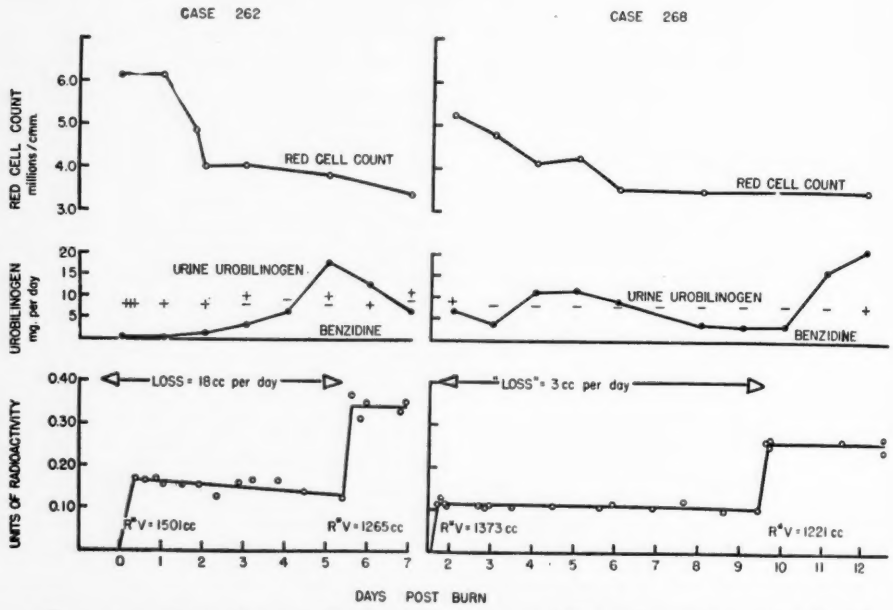


CHART 10.—Cases 262 and 268: Red cell counts, urobilinogen excretion and radioactivity data indicating mild cell destruction in two severely burned, aged patients dying of their injuries (male, age 64, 85 per cent total, 58 per cent third degree; female, age 83, 62 per cent total, 22 per cent third degree).

The rapidly developing peripheral anemia indicated by the fall in red cell count was not accompanied by a comparable decrease in red cell mass and is, therefore, a false anemia. Both patients showed an increase in urobilinogen excretion, Case 262 also showing considerable excretion of benzidine-reacting pigment in the urine. This evidence of red cell destruction was accompanied by a slight fall in red cell mass (R*V) in Case 262. In Case 268 the average loss of 3 cc. of cells per day is within the limits of error of the method.

The radioactivity concentrations in both cases, which resulted from active transfusions given soon after injury, remain approximately constant; the slight fall in Case 262 may be significant, which would indicate active cell regeneration during the period of destruction.

red cell destruction, as indicated in volume measurements, and even jaundice.* The other three, however, all showed evidences of cell destruction which seem to be disproportionally small in relation to their massive and fatal injuries.

* We have seen little clinical jaundice. It is our impression that in a group of sulfanilamide-treated patients clinical jaundice is more frequently encountered than in a series treated with penicillin. This may be traceable to the fact that the blood pigment released in the blood stream by early hemolysis can be metabolised efficiently by the liver if it is not also suffering under the load of an hepatotoxin, such as a sulfonamide.

Case 262.—An elderly man showed a slight rise in urobilinogen excretion but his volume changes showed little evidence of red cell destruction. Multiple determinations of his cell radioactivity after radioactive transfusions showed a slight lowering of activity compatible with slow destruction of the donor cells (Chart 10).

Case 268.—(Chart 10): An aged woman showed no benzidine-positive material in the urine, an unique finding for such an extensive burn (62 per cent total) which was fatal in 13 days. The cell volume data and cell activity data show no departure from normal.

Case 231.—A male, age 36, with a skin burn of 68 per cent, 39 per cent of his total surface being full-thickness, succumbed on his sixth day to the pulmonary effects of the burn and disordered fluid metabolism, with pulmonary edema. An iron build-up curve carried out during his five days of life after the injury showed an essentially normal utilization, a departure from the data recovered from the first two patients of the previous group (Cases 210 and 217). This patient also showed an increase in urobilinogen excretion and a strongly positive benzidine reaction in the urine as evidence of hemolysis.

TABLE XIII

CELL CHARACTERISTICS

Case	% Burn Total/3°	Day Post-Burn	R.B.C. Millions	Hb. Gm. %	Hematocrit % Cells	M.C.V.* Cμ§	M.C.H.† γγ ‖	M.C.H.C.‡ %
Normal			4.5–5.0	16.0 ± 2	47 ± 5	90–105	32–38	26–30
170	15/17	9	3.9	11.0	41	105	28	26
		15	4.3	12.4	44	103	30	28
260	28/12	7	3.1	12.6	36	115	40	35
		34	2.8		34	120		
135	25/15	14	3.7		37	100		
149	72/38	5	3.5	12.0	39	111	38	34
155	41/26	1	4.3	15.1	50	116	35	30
		16	4.1	12.6	36	93	32	35
		30	4.0	12.6	56	140	32	23
		40	4.8	17.5	48	100	35	35
		55	4.3	10.6	48	110	25	23
210	31/25	11	2.6	8.0	25	95	31	33
		28	3.5	11.5	38	100	33	33
217	78/45	4	3.9	13.0	34	87	34	39
		18	3.5	12.0	35	101	35	34

Explanation of Table:

* M.C.V. = Mean Corpuscular Volume.

† M.C.H. = Mean Corpuscular Hemoglobin.

‡ M.C.H.C. = Mean Corpuscular Hemoglobin Concentration. The normals are taken from Wintrobe, *et. al.*,[5] except for M.C.V. which is based on our normal R.B.C. of 4.5–5.0 million.

§ Cμ = Cubic micron (.001 mm. = 1μ).

‖ γγ. = One thousandth of a gamma (.000001 mg.).

3. OTHER HEMATOLOGIC OBSERVATIONS

The red cell characteristics encountered at various times during the care of patients is shown in Table XIII. These data are representative of the whole group. Some macrocytosis with slight tendency to hyperchromia are the only significant abnormalities.

COMMENT

Anemia or a decrease in circulating red cell mass is a complication of the deep burn. All of our patients developing a significant anemia, have had burns with full-thickness destruction, usually of 10 per cent or more, of the body surface. Patients with superficial burns of more than 20 per cent of the

body surface may exhibit a false anemia due to hemodilution from an increased plasma volume. In patients with either full-thickness or superficial burns, this false anemia must be differentiated clinically from the true anemia. In the false anemia the treatment depends upon with-holding fluid and allowing renal excretion to keep pace with the resorption of edema fluid. In the true anemia red cells in the form of whole blood transfusions are needed.

In the patient with an extensive full-thickness burn the true and false anemias may coexist. Examination of the patient clinically for stage of edema formation or resorption, of the urine output for diuresis, of the serum for protein dilution, and of the peripheral erythrocyte indices for red cell concentration provides good clues as to the extent of the false anemia. There is no wholly satisfactory substitute, however, for an objective measure of the red cell mass by any one of the several available methods, and such measurements should form a part of the clinical care of an extensively burned patient.

The true anemia of burns develops in three stages; only one or two of the stages may be encountered. The first stage stems from the initial hemolysis connected with the injury and is the least severe of the three. The second stage takes place during the first week or ten days. It may be, in part, related to injury of the red cells, but has other causes, including depression of the bone marrow. The third stage appears in the third or fourth week, has multiple causes, including hemorrhage from the wound, and may persist until the wounds are closed. Between the second and third stages a transitory period of positive red cell balance has been observed in some patients.

From the practical point of view the development of anemia must be constantly suspected in severely burned patients, its extent accurately measured and the red cell deficit met with whole blood transfusions. At the peak of destruction in the second and third stages as much as 500 cc. of blood (250 cc. of cells) may be required each day. In addition, the blood lost in grafting must be replaced. If only grafts are cut, but 100 to 150 cc. may be lost. If excision of the wound is to be carried out before grafting, preparation should be made to replace much larger quantities. Bleeding from excision of recently burned, freshly edematous wounds is limited to a relatively few large vessels, while that from older, more inflamed than edematous wounds may be profuse from numerous small vessels. As much as 1,750 cc. of whole blood has been lost during the excision of extensive, inflamed wounds.

The recent suggestion of Moyer and Coller[14] that whole blood rather than plasma be employed to maintain circulating blood volume after severe burns involves consideration of *Rh* typing, the effect of high hematocrit on blood viscosity and cardiac output, and other questions which are beyond the repair of anemia. The amounts of red cells employed in such treatment far exceed the requirements imposed by the burn anemia, and any results claimed for such therapy cast little light on the extent of this anemia.

Of the factors which may participate in producing the red cell loss in the three clinical stages, the following deserve mention:

1. *Early Hemolysis and Cell Fragility:* Our findings corroborate the pres-

ence of early severe hemolysis in most (but not all) deeply burned patients. The total mass of cells involved in this initial hemolysis does not exceed 10 per cent of the red cell mass. We have no evidence that the increased fragility is due to the heat and not to some other disturbance, for example, in fluid distribution or enzyme activity, which continues to operate for some time after injury.

2. *Blood Destruction by Un-neutralized Plasma Antibodies:* In spite of the theoretic possibility, we have no convincing evidence that un-neutralized plasma antibodies played a rôle in cell destruction in any of the patients included in the present study.

3. *Blood Loss through an Open Wound:* As the burned tissue sloughs away, an open wound is produced which may cover a large area of the patient's body surface. It is clear that any operative procedure, however minor, produces red cell losses from this large surface. It is not so obvious, however, to what extent red cells may leak from this wound into the dressing, there to be digested by bacteria and the hemoglobin converted into a metabolic end-product which removes its color, obscuring the extent of the cryptic hemorrhage.

4. *Infection:* All of our patients showing hidden progressive disappearance of red cells had large open infected wounds. Contamination and subsequent infection is truly inevitable in any deep burn, even with the massive use of penicillin and other agents directed at the infecting micro-organisms.[15] Yet not all of the patients with extensive infected wounds developed anemia. No difference in the types of infecting organisms was noted in those patients developing anemia from those with none.

Infection is doubtless important but until a third degree burn of considerable extent can be maintained without infection by the use of some, as yet unknown, antibacterial agent, it is impossible to separate the factors of iron deposition in the inflammatory barrier and infectious toxemia from the rôle played by a slow-leaking hemorrhage from the large open wound.

5. *Disordered Iron Metabolism and Depressed Marrow Function:* The impaired elaboration of radioactive iron into the hemoglobin of circulating red cells of our patients points to disorder of iron metabolism and depressed bone marrow function as an important factor in the anemia of burns. (This statement is made in spite of the fact that in one patient, later dying of his injuries, a normal utilization was observed.) The low reticulocyte counts generally encountered in our patients and the occasional macrocytosis confirm a depressed marrow activity.

In addition to the mechanism studied by Wintrobe, there are in burned patients other possible causes for disorder of iron metabolism and hemoglobin synthesis. Gastro-intestinal tract function is grossly disturbed. Edema, ulceration, gastritis, all may play a rôle. Liver function may be altered. These factors might lessen iron absorption and hemoglobin synthesis. The impaired utilization of radioactive iron of our patients could not have been due to impaired absorption, however, since the iron was injected intravenously.

6. *The Alarm Reaction:* It is impossible at present to do more than speculate on the importance of the alarm reaction in red cell destruction and bone

marrow depression. Prolonged negative nitrogen balance with transient negative potassium balance has been found in all but one of our cases.[16] If this is an outward manifestation of cell breakdown and the release into extracellular fluid of substances normally intracellular, it is conceivable that the red cells may partake of the process, or perhaps the nucleated erythrocyte precursors in the marrow which more closely resemble other body cells in their vital processes. Another possible explanation is that protein synthesis is blocked; the formation of globin may be retarded, hindering hemoglobin production.

That the alarm reaction or adaptation syndrome[17] is in some manner implicated in the progressive anemia is suggested by the observations that the one patient not showing a negative nitrogen balance did not develop an anemia, and by the rapid increase in cell disappearance following operation (Case 210). Operation is a well-known stimulus of the alarm reaction.

7. *Multiple closely placed transfusions* were occasionally found to be disappointing in restoring red cell volume. On the other hand, no evidence was found to support the contention that transfusions inhibit marrow activity. Undoubtedly the gradual replacement of losses as they occur is more economical of blood as well as more physiologic. Delay in blood replacement is followed by substitution of extracellular fluid for the lost red cell mass, with restoration of total blood volume and a low peripheral red cell concentration. Delayed replacement produces an expanded blood volume which results in an increased cardiovascular load and, possibly, compensatory destruction of a portion of the infused cells.

SUMMARY

An anemia of varying severity may be present in burned patients. If not repaired, it will retard healing, prolong hospitalization and jeopardize the healing of skin grafts. This anemia has been investigated by serial studies of the red cell mass and bone marrow activity, employing a radioactive isotope of iron and by measurements of pigment excretion.

The anemia is found only in patients with full-thickness burns; it may, in rare cases, surprise one by its absence, even during the acute phase in patients with fatal burns.

True reductions in red cell mass must be distinguished from the false anemia of hemodilution encountered early in the patient's course. The therapy of each differs.

Multiple influences including hemolysis, cryptic wound hemorrhage, iron deviation, gastro-intestinal absorption, infection and marrow depression enter into the etiology of the anemia.

Its anticipation and early replacement is far preferable to late recognition and delayed transfusion.

While clinical observation may provide the astute surgeon with many clues as to the state of the red cell mass, and may help to distinguish true anemia from false (hemodilution) anemia, there is no adequate substitute in the clinical care of a severely burned patient, for serial objective measurements of the red cell volume.

REFERENCES

1 Altemeier, W. A., and Carter, B. N.: Infected Burns with Hemorrhage. ANNALS OF SURGERY, **115,** 1118, 1942.

2 Shen, S. C., Ham, T. H., and Fleming, E. M.: Studies on the Destruction of Red Blood Cells. New England J. Med., **229,** 701, 1943.

3 Colebrook, L., *et al.:* Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942-43), Medical Research Council, Special Report Series 249. London: His Majesty's Stationery Office, 1944.

4 Menkin, V., and Menkin, M. F.: The Accumulation of Iron in Tuberculous Areas. J. Exper. Med., **53,** 919, 1931.

5 Cartwright, G. E., Lauritsen, M. A., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.: The Anemia of Infection. I. Hypoferremia, Hypercupremia, and Alterations in Porphyrin Metabolism in Patients. J. Clin. Invest., **25,** 65, 1946.
Cartwright, G. E., Lauritsen, M. A., Humphreys, S., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.: The Anemia of Infection. II. The Experimental Production of Hypoferremia and Anemia in Dogs. J. Clin. Invest., **25,** 81, 1946.

6 Moore, F. D., Evans, R. D., and Cope, O.: The Redistribution of Body Fluids in the Extracellular Space in Response to Thermal Trauma and Treatment. In preparation.

7 Abbott, W. E., Hirshfeld, J. W., and Meyer, F. L.: Metabolic Alterations following Thermal Burns. II. Changes in the Plasma Volume and Plasma Protein in the Convalescent Phase. Surg., Gynec. & Obst., **81,** 25, 1945.

8 Stead, E. A., Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume. Am. J. Physiol., **132,** 411, 1941.

9 Hahn, P. F., Ross, J. F., Bale, W. F., Balfour, W. M., and Whipple, G. H.: Red Cell and Plasma Volumes (Circulating and Total) as Determined by Radio-Iron and Dye. J. Exper. Med., **75,** 221, 1942.

10 Peacock, W. C., Evans, R. D., Irvine, J. W., Jr., Good, W. M., Kip, A. B., Weiss, S., and Gibson, J. G., 2nd: The Use of Two Radioactive Isotopes of Iron in Tracer Studies on Erythrocytes. J. Clin. Invest., in press.

11 Watson, C. J.: Studies of Urobilinogen. I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces. Am. J. Clin. Path., **6,** 458, 1936.

12 Gilligan, D. R., Altschule, M. D., and Katersky, E. M.: Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solutions. J. Clin. Invest., **20,** 177, 1941.

13 Cope, O., Nathanson, I. T., Rourke, G. M., and Wilson, H.: Management of the Cocoanut Grove Burns at the Massachusetts General Hospital. Metabolic Observations. ANNALS OF SURGERY, **117,** 937, 1943.

14 Moyer, C. A., Coller, F. A., Iob, V., Vaughan, H. H., and Marty, D.: A Study of the Interrelationship of Salt Solutions, Serum and Defibrinated Blood in the Treatment of Severely Scalded, Anesthetized Dogs. ANNALS OF SURGERY, **120,** 367, 1944.

15 Langohr, J. L., Owen, C. R., and Cope, O.: A Comparison of the Bacterial Flora of Burn Wounds Treated with Sulfonamides and Penicillin. In preparation.

16 Cope, O., Langohr, J. L., and Moore, F. D.: The Rôle of Exudate Losses in the Protein and Electrolyte Balance in Burn Patients. In preparation.

17 Seyle, H.: The General Adaptation Syndrome and the Diseases of Adaptation. J. Clin. Endocrinology, **6,** 117, 1946.

ASCORBIC ACID, RIBOFLAVIN, THIAMIN, AND NICOTINIC ACID IN RELATION TO SEVERE INJURY, HEMORRHAGE, AND INFECTION IN THE HUMAN*

S. M. Levenson, M.D., R. W. Green, M.D., F. H. L. Taylor, Ph.D., P. Robinson, B.S., R. C. Page, B.S., R. E. Johnson, M.D., Ph.D., AND C. C. Lund, M.D.

Boston, Massachusetts

Careful studies of ascorbic acid and of vitamin K in relation to surgical conditions have been reported in numerous publications during the last few years. Few similar studies of other vitamins have been made. In the meantime, all known vitamins are being used in the care of surgical patients with increasing frequency and in increasing doses. Recent work in the laboratory has shown that many vitamins play much more fundamental rôles in the animal organism than merely preventing or curing the well-known syndromes of scurvy, beri-beri, pellagra, or hypoprothrombinemia. For instance, thiamin and nicotinic acid both play fundamental rôles in the enzyme systems that control the metabolism of carbohydrates. Riboflavin is also important for the carbohydrate metabolism and, in addition, has a function associated with amino-acid metabolism. Ascorbic acid is said to have a fundamental rôle in the formation of adrenocortical hormone. These functions indicate that these four vitamins play important rôles in connection with recovery from shock, injury, and acute infections, since disturbances in the metabolism of carbohydrate, protein, and of adrenocortical hormones are caused by these conditions. Thus, Govier[1] has found the mortality of normal dogs exposed to a standardized type of hemorrhagic shock was reduced when thiamin was given in large doses before or after bleeding. In addition, dogs deficient in thiamin were particularly susceptible to death from hemorrhagic shock. Sayers, *et al.*[2] have found that there is a sudden fall in the ascorbic acid content and a slower fall in cholesterol content of the adrenal glands in hemorrhage and in hemorrhagic shock in rats and guinea-pigs. Uzbekov,[3] and Clark and Rossiter,[4] earlier, had found decreases

* From the Burn Assignment of the Surgical Services, the Thorndike Memorial Laboratory and the Second and Fourth Medical Services (Harvard) of the Boston City Hospital, the Departments of Surgery and of Medicine of the Harvard Medical School, and the Fatigue Laboratory of the Harvard Business School.

The work described in this paper was done in part under contracts recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

The preparation of the data for publication was aided by a grant from the John and Mary E. Markle Foundation.

Read before the American Surgical Association, April 2–4, 1946, Hot Springs, Virginia.

in the ascorbic acid content of the adrenal cortex in burned guinea-pigs and rabbits, respectively.

Andreae, and his associates,[5] have studied the excretion of riboflavin in 23 cases of burns and injuries. It is not stated whether shock was encountered in any instance. This short preliminary report is quoted in full because of its importance.

"The 24-hour urinary excretion of riboflavin was followed in 23 patients who had suffered fractures and burn injuries and whose daily intake level of this vitamin was kept constant at 5.0 mg. by supplementation with crystalline riboflavin. Whereas about one-half of the ingested riboflavin is retained at this intake level in health, patients with acute injuries characteristically showed a marked retention during the initial three to five days after injury. This state was followed by a period of similar duration when there occurred an increased riboflavin loss as shown by the excretion rate. After about ten days following the injury, the riboflavin balance returned to normal. This would suggest that the vitamin retained during the first period was not utilized or destroyed, but was stored in some way and subsequently released. Observations made on these patients during convalescence demonstrated a retention of nitrogen. This correlation was statistically analyzed and found to be highly significant so that for each gram of nitrogen retained 0.30 mg. of riboflavin was retained over the normal base line."

The present study is concerned with the alterations in the blood level of ascorbic acid, and in the urinary excretion of ascorbic acid, thiamin, riboflavin, and of n-methyl-nicotinamide, in patients with severe injury, hemorrhage, or infection.

METHODS

The patients studied were cared for by the members of the "Burn Assignment" in a Metabolic Ward which was supplied with special nurses. The dietary calculations were made by a research dietitian. All hematologic and routine chemical determinations were by methods previously published from the Thorndike Memorial Laboratory.[6] Plasma ascorbic acid determinations were by the method of Mindlin and Butler.[7] The determinations of vitamin outputs were made in the Harvard Fatigue Laboratory using the field methods[8] developed there. These tests were made on timed morning specimens collected at least 14 hours subsequent to any vitamin administration. Vitamin supplements were given orally in the form of ascorbic acid tablets, and of "Multicebrin" capsules. These contain in each capsule: thiamin chloride, mg. 3.0; riboflavin, mg. 3.0; pyridoxine hydrochloride, mg. 1.5; pantothenic acid, mg. 5.0; nicotinamide, mg. 25; ascorbic acid, mg. 75; distilled natural tocopherols, mg. 10; vitamin A, 5,000 U.S.P. units; and vitamin D, 1,000 U.S.P. units. Vitamins were given intravenously in the form of single or multiple vitamin preparations. Saturation tests of vitamins were made as follows: The test doses were given after the collection of a fasting specimen of blood and a fasting hour specimen of urine. Specimens of blood and of urine were then collected at intervals of

one-half, one, two, three, and four hours. Two different test doses were used. One, named a "high test" contained not less than: ascorbic acid, one gram, thiamin chloride, 20 mg., riboflavin, 12 mg., and nicotinamide, 450 mg. The other, the "low test" contained ascorbic acid, 250 mg.; thiamin chloride, 5 mg.; riboflavin, 3 mg.; and nicotinamide, 50 mg. These "low" saturation tests have been used previously in studies of soldiers in all parts of the world.[8] Both "high" and "low" saturation tests have been studied on healthy laboratory personnel at the Boston City Hospital and the findings of these studies will be published shortly.[9]

Table I lists the patients with their diagnosis and the outcome of their treatment.

TABLE I

PATIENTS' DIAGNOSES AND OUTCOME OF TREATMENT

Case No.	Patient	Age	Sex	Shock	Diagnosis
1.	P. D.	24	M	0	Bullet wounds of jaw, neck, and abdomen with fractured jaw, perforated trachea, and perforated hepatic flexure. Operation—Death—Autopsy
2.	W. B.	33	M	+	Bilateral crush injuries both lower legs. Operation—Recovery
3.	P. J.	15	M	0	Bullet wounds of abdomen and chest, with lacerations of liver, perforated duodenum, ruptured right kidney, and hemopneumothorax. Operation—Death—Autopsy
4.	S. A.	58	M	+	Traumatic rupture right kidney, head injury, compound fracture both bones right lower leg. Operation—Recovery
5.	K. R.	56	M	+	Massive hematemesis, ? etiology. Operation—Recovery
6.	J. B.	46	M	+	Perforated gastric ulcer, peritonitis. No operation—Death—Autopsy

CASE REPORTS

CASE 1.—P. D., a 24-year-old white male, with a noncontributory past history, was admitted shortly after receiving bullet wounds of the jaw and abdomen. Examination on entry revealed a well-developed and well-nourished man. Blood pressure 115/80; pulse 132 of good quality; respirations 18. There was a small bullet hole on the right side of the lower jaw through which there was a fair amount of blood oozing. In addition, the patient was coughing up moderate quantities of blood. The lung fields were clear and resonant. Just above the right posterior iliac crest, about two inches from the midline, was another small bullet hole. Anteriorly, there was a small hematoma just to the left of the midline below the costal margin. The abdominal wall was rigid, and peristalsis was absent.

Fourteen hundred cubic centimeters of blood, 1,650 cc. of saline, and 1,000 cc. of 5 per cent glucose in water were administered intravenously in the first four hours after entry. The blood pressure and pulse remained good. At the end of this time, operation was performed.

Abdominal exploration revealed that the hepatic flexure had been perforated posteriorly and anteriorly. Resection of the damaged bowel was carried out and a primary end-to-end anastomosis made. The bullet was removed from the anterior abdominal wall. Exploration of the neck revealed that the second bullet had lodged in the right posterior lateral aspect of the larynx. It was removed and the resulting tracheal fistula packed with gauze. During the operative procedure, the patient was given 500 cc. of blood and 500 cc. of saline, and the blood pressure and pulse remained good. The urine output was satisfactory. Postoperatively, slight oozing of blood through the mouth continued and constant pharyngeal suction was carried out. The temperature varied from 100° to 102° F. rectally; the blood pressure and pulse re-

mained good, but there was sudden respiratory distress and asphyxia five hours postoperatively. Postmortem examination revealed the cause of death to have been aspiration of blood.

No vitamins were given at any time. The plasma ascorbic acid concentration at one and at three hours after entry was zero. At seven hours after entry it was 0.3 mg./100 cc. of plasma. Hourly excretion rates of the vitamins at 2.5 and 4.5 hours after entry were as follows: thiamin 0.3 and 10 micrograms per hour; riboflavin, 26 and 17 micrograms per hour; and the n-methyl-nicotinamide, 0.35 and 0.68 milligrams per hour.

COMMENT: A previously well-developed and well-nourished healthy male with major injuries but with no shock and with a good urine output. The plasma ascorbic acid was zero on two occasions prior to operation, but rose slightly during recovery from operation. The first determination of thiamin output was low but the second determination of thiamin and both determinations of riboflavin and of the n-methyl-nicotinamide were normal.

CASE 2.—W. B., a 33-year-old white male, with a noncontributory past history was admitted at 6 P.M., shortly after receiving crush injuries to both legs when he fell under a street car when intoxicated. Examination revealed a well-developed and well-nourished man, semiconscious. His skin was pale and cold, his blood pressure 70/50, pulse of fair quality. Both lower legs were crushed just below the knees and, in addition, there was a simple intracapsular fracture of the neck of the left femur. Leather belts had been applied as tourniquets at the scene of the accident. These were replaced by rubber tourniquets. He was given mg. 30 of morphine and an intravenous of saline, plasma, and of whole blood started. The blood pressure rose to 90/50 in 30 minutes and to 110/50 in the next one and one-half hours. His pulse was 100 at this time and of good quality. The urine output was good.

During the first six hours he was given a total of 1,000 cc. of plasma, 2,000 cc. of blood, and 2,000 cc. of saline. At this time, under cyclopropane anesthesia, bilateral, low thigh, guillotine amputations were done. The wounds were left open and dry pressure dressings applied. A Kirschner wire was inserted through the lower end of the left femur to serve as a means of applying traction to the fractured left femoral neck. During the operation he was given 1,000 cc. of additional blood. His blood pressure remained good until just after the operation, when it fell for a brief period to 70/50, at the time of a mild hemolytic transfusion reaction. Thereafter there were no further periods of shock. Penicillin, 20,000 units every two hours intramuscularly, was started on entry and continued for 15 days. The temperature which during the first few days rose as high as 102° F. rectally, became normal by the seventh day and remained normal thereafter. The wounds were secondarily revised and closed on the 17th and 28th days. During the first five days he was fed almost entirely intravenously with Amigen* and glucose in quantities sufficient to give him 20 Gm. of nitrogen and 3,000–4,000 calories daily. Subsequently he took food well by mouth. This diet contained approximately the same amounts of nitrogen and calories as given previously. The nitrogen output varied between 17 and 42 grams daily. The nitrogen balance and vitamin data are given in Charts 1 and 2.

COMMENT: The ascorbic acid concentration on three occasions during the first 12 hours was zero. At 16 hours, without any ascorbic acid having been given, the plasma level had risen to 0.3 mg. per 100 cc. At that time a "high" saturation test was performed. (See Chart 2.) The plasma response to this was lower than is seen in normal individuals. The excretion

*The Amigen was kindly supplied by the Mead-Johnson Corporation.

was also low, being less than 50 mg. The next day this test was repeated. The plasma curve was almost identical, but nearly 300 mg. was excreted. This is still below the usual excretion of a fully saturated individual. The

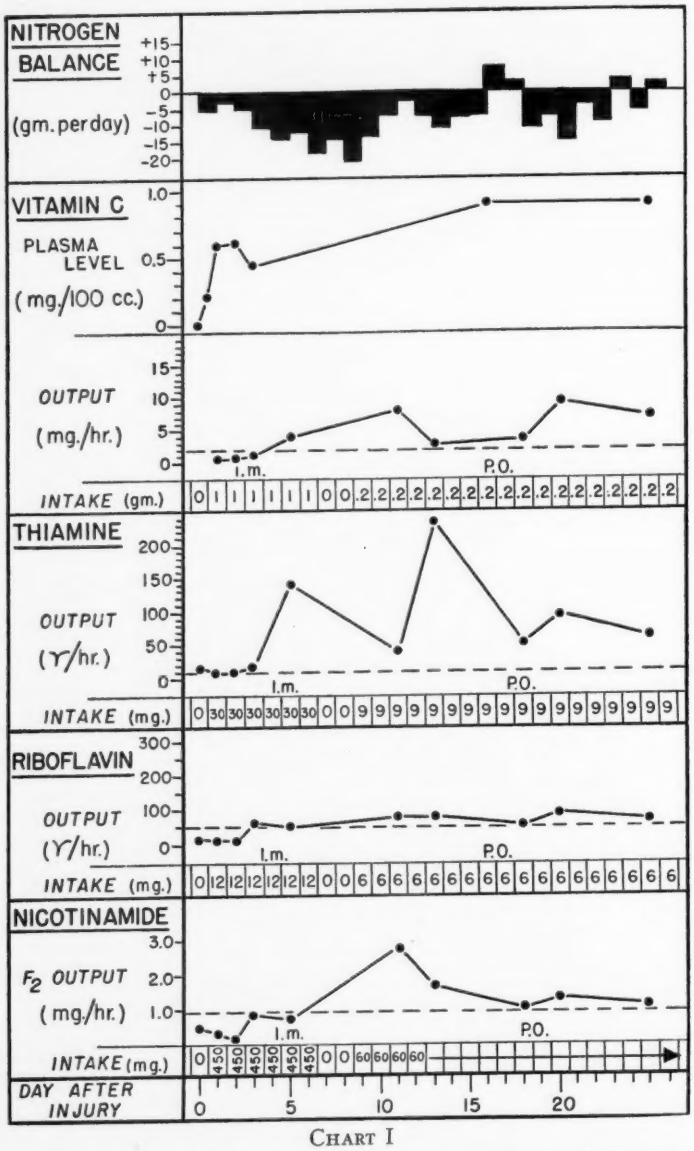


CHART I

The dotted lines indicate the *average* output of normal men on normal diets who are taking no supplementary vitamins.

fasting hour excretions of the three "B" vitamins and ascorbic acid were at low levels immediately after injury and, what is important, remained at these low levels for five days despite large doses given daily, as shown by Chart 1.

CASE 3.—P. J., a 15-year-old healthy high school boy, was admitted shortly after receiving a bullet wound of the abdomen. Examination revealed him to be well-developed and well-nourished. He was somewhat drowsy but fully conscious and rational. Blood pressure 90/40. His chest was clear and resonant throughout, and his abdomen was spastic, with absent peristalsis. Just above the umbilicus in the midline was the entrance wound of a bullet and posteriorly over the region of the right kidney was the exit wound. Both wounds were bleeding slowly.

He was given mg. 10 of morphine, and intravenous glucose in saline was started. After 400 cc. had been given in a period of a half hour, the blood pressure rose to 140/78. His pulse at this time was 108 and his respirations 20. In the next 1.5 hours he was given 500 cc. of blood, following which, under spinal anesthesia supplemented by cyclopropane, operation was carried out. It was found that the left lobe of the

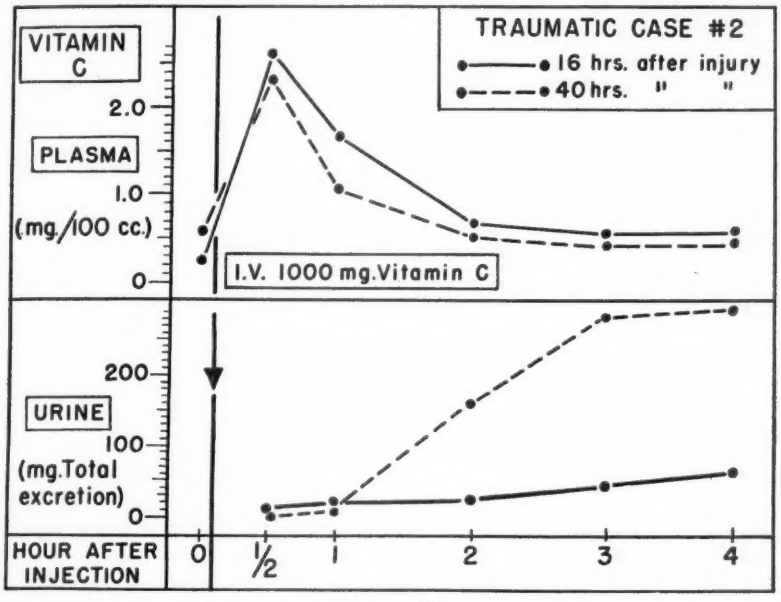


CHART II

Saturation test—Ascorbic Acid Intravenously

liver, the duodenum, the right lobe of the liver, the right kidney, and the right pleural cavity had all been perforated by the bullet. Crushed liver tissue was removed, the two perforations in the duodenum repaired, and the kidney removed. Drains were inserted down to the kidney bed and to the liver wound. The wound of entrance was excised and packed open with gauze. The wound of exit was also excised and was found to connect with the right pleural cavity. There was about one pint of blood in the pleural cavity and during exploration of the wound air was sucked in during inspiration. A gauze pack was inserted to control the aspiration of air. During the operation, the patient was given additional blood and saline. The blood pressure and pulse remained good, and thereafter there was no fall in blood pressure.

Postoperatively, he was given 25,000 units of penicillin every two hours for the first ten days. Five grams of sulfadiazine were given by clysis daily for the first three days and orally thereafter. Gastric drainage was instituted immediately after operation, and he was given 150 grams of protein hydrolysate and sufficient glucose intravenously to bring his caloric intake to 3,000 calories. Vitamins were started on the first postoperative day, as described below.

His postoperative course was satisfactory for the first week. He then began to run an afternoon fever of 102° F., but had no specific localizing signs. His urine output was three liters, or more, per day. On the 10th postoperative day, under cyclopropane anesthesia, the pack from the epigastric wound was removed, as was the drain from the liver and one of the drains to the kidney region. Culture of the wounds revealed *B. pyocyaneous.* The pack was taken out of the wound of exit, which was found to still connect with the pleural cavity. Consequently, a gauze pack was reinserted and the patient left the operating room in good condition. About ten hours after the dressing change the patient appeared considerably sicker and was markedly dyspneic. Examination revealed signs consistent with a pneumothorax in the right chest. The abdomen was soft and not tender. Roentgenograms confirmed the diagnosis of pneumothorax. Five hundred cubic centimeters of air were removed from

TABLE II

CASE 3: P. J.—BULLET WOUNDS OF LIVER, DUODENUM, AND KIDNEY

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Temperature		103°	102°	102°	101°	104°	101°	102°	101°	105°	102°	105°	105°	1 5°
Caloric intake	550	2950	2900	3050	3000	3000	3000	3000	3000	3000	3000	2500	1100	2250
Nitrogen intake (grams)	7	23	26	24	24	24	24	24	24	24	24	19	0	3
Nitrogen output (grams)		15	25	25	27	22	24	19	25	22	39	16	37	9
Plasma protein (grams/100 cc.)	5.7	4.7		5.6								6.8		
Plasma ascorbic acid (mg./100 cc.)	0.6	0.6		0.6		0.5			0.8		1.1			
Urine ascorbic acid (mg. per hour)		6		4		17		24			13			
Urine thiamin (micrograms per hour)		28		35		225		510			200			
Urine riboflavin (micrograms per hour)		105		17		57		64			68			
Urine n-methyl-nicotinamide (micrograms per hour)		0.3		0.6		3.2		2.6			1.4			

Vitamins were administered intravenously in the following daily doses from the 1st to the 13th day: Ascorbic acid, G 1.0; thiamin mg. 30; riboflavin, mg. 12; and nicotinamide, mg. 450.

the right chest, without significant effect on the dyspnea. His temperature had risen to 105°F. rectally. Penicillin which had been discontinued following the dressing, was resumed, and, in addition, sulfamerizine was begun, the sulfadiazine also having been omitted at the dressing change. Roentgenograms the following morning revealed the pneumothorax to be less and the lung fields to be clear except for some atelectasis of the right lower lobe. There was neither cyanosis nor dyspnea. The temperature continued high despite repeated alcohol sponges. Two lumbar punctures were negative. He gradually became weaker and died on the 14th day. Autopsy revealed no definite cause of death. The nutritional and vitamin data are given in Tables II and III.

COMMENT: This boy had a severe injury but was in excellent muscular training and nutritional condition. He did not go into shock at any time. Early, his ascorbic acid concentration in the plasma remained relatively high, being 0.6 mg. per 100 cc. of plasma on two occasions prior to any vitamin supplementation. He was given one gram of ascorbic acid; thiamin

30 mg.; riboflavin 12 mg.; and nicotinamide 450 mg. daily beginning on the first hospital day. On the first, third, seventh, and eighth days the vitamins were given in rapid injections for "high" saturation tests. On all other days they were given in a slow intravenous drip. The plasma ascorbic acid concentration remained between 0.5 and 1.1. The plasma levels of ascorbic acid in the first two tests were low but in the fourth test were normal. The four-hour urine excretions of ascorbic acid, thiamin, and riboflavin during the saturation tests were low on the third day, normal on the seventh day. The excretion of n-methyl-nicotinamide was normal on both occasions.

The "fasting hourly" excretions of ascorbic acid, thiamin, and n-methyl-nicotinamide were much lower on the first and third postoperative days than on the fifth and subsequent days. In the case of riboflavin, the first day excretion was higher than that on subsequent days.

TABLE III

CASE 3: P. J.—"HIGH" SATURATION TESTS

Days	Plasma Ascorbic Acid Milligrams Per 100 Cc. Hours					Urine—Output in Four Hours			
	Fasting	0.5	1	2	4	Ascorbic Acid (Milligrams)	Thiamin (Milligrams)	Riboflavin (Milligrams)	N-methyl-nicotinamide (Milligrams)
1.	0.6	1.9	1.7	1.5	1.0				
3.	0.6	1.4	1.3	1.3	0.6	108	4.0	0.6	23
7.						484	17	10	56
8.	0.8	3.1	2.9	2.7					

Saturation test doses: Ascorbic acid, G. 1.0; thiamin, mg. 30; riboflavin, mg. 12; and nicotinamide, mg. 450.

CASE 4.—S. A., a 58-year-old laborer, previously well, except for chronic bronchitis, was seen three hours after having been struck by an automobile. Examination on admission revealed a well-developed, well-nourished man with a compound fracture of both bones of the right lower leg and a laceration over the right eye. There were no external bruises elsewhere, and examination was otherwise negative. Blood pressure 80/50, pulse 90. During the next five hours he was given 900 cc. of plasma, 1,500 cc. of whole blood, 900 cc. of saline, and 50 grams of glucose. His blood pressure varied between 70/50 and 110/60, with his pulse remaining about 90. His abdomen, which had previously been soft, gradually became generally spastic and tender. Catheterization revealed grossly bloody urine. A spinal puncture revealed bloody fluid but a normal pressure of 160 mm.

Under spinal anesthesia, supplemented with cyclopropane, gas and ether, celiotomy was performed. There was about 200 cc. of blood in the peritoneal cavity but no injury to any interperitoneal organs. The blood had dissected up from the right retroperitoneal area where there was a large hematoma. The celiotomy wound was closed and a laparotomy exposed the right kidney, which was found to be ruptured completely across the pelvis. It was removed. The wound was packed and partially closed. During the operation the patient was given 1,000 cc. of whole blood; 1,200 cc. of saline and bicarbonate by clysis; and 50 grams of glucose intravenously. His

blood pressure, which was between 70/40 and 90/60 during the operation, rose immediately after the kidney was removed to 120/84. Thereafter there were no periods of shock.

The wound of the right lower leg was then irrigated and débrided. Kirschner wires were passed above and below the fracture line of the tibia and a plaster encasement was applied. The wound was not closed, even in part.

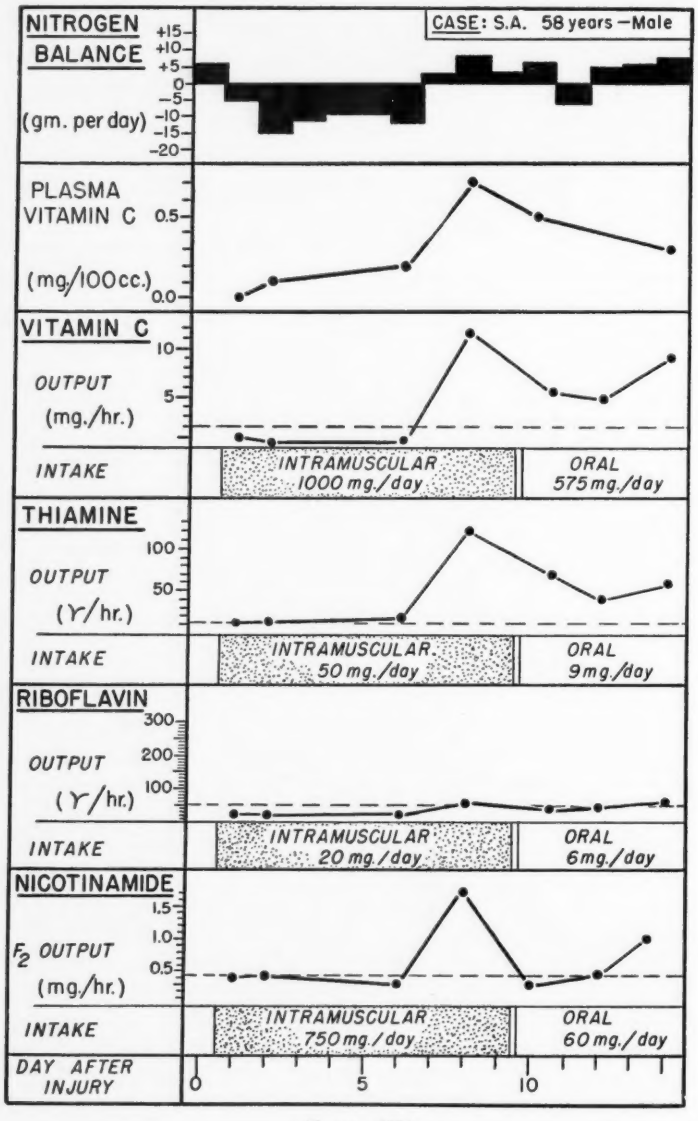


CHART III

Two hours postoperatively, 12 hours after injury, his temperature had risen to 106°F. rectally. Vigorous cold alcohol sponges were administered, and the temperature fell to 102.6° F. in the next one and one-half hours. At this time, a neurologic examination was negative. A second lumbar puncture revealed that the pressure had risen

to 300 mm. Repeated therapeutic lumbar punctures were performed during the next few days. After the sixth day the spinal fluid pressure and spinal fluid were normal.

Eighteen hours postoperatively, he became moderately dyspneic and cyanotic. A chest roentgenogram revealed diffuse mottling of the upper left lobe. Penicillin, 20,000 units, was given intravenously every two hours, and oxygen was administered by a tent. Within 36 hours he had improved, the dyspnea had disappeared, and only slight cyanosis remained. A chest film ten days later revealed the lung fields to be clear.

The clinical course after the second day was uncomplicated except for minimal infection of the kidney wound. The temperature ranged between 101° and 102°F. rectally until the 12th day, and after the 14th day was normal. Penicillin was discontinued on the 15th day. He was allowed to get out of bed daily after the seventh day, and felt very well. The hemoglobin which had been 90 per cent on entry fell gradually to 67 per cent by the eighth day. Two thousand cubic centimeters of whole blood was given in the next six days, the hemoglobin rising to 95 per cent.

During the first week he was given nourishment for the most part by the intravenous route. This consisted of plasma and glucose on the first day with Amigen and glucose for the next six days. The caloric intake ranged between 1,500 and 1,700 calories, with an average of 1,550. The nitrogen intake ranged from 14 to 17 grams, with an average of 15. The nitrogen output in the urine was 10 grams the first day, 30 grams the second and gradually decreased to 21 grams on the sixth, followed on the seventh day with an output of only 15 grams. There were no stools during this period. In the second week, oral feeding only was used, with an intake of from 2,700–4,100 calories, with an average of 3,100. The nitrogen intake ranged from 13 to 25 grams, with an average of 18. The nitrogen output ranged from 12 to 18 grams, with an average of 15.

The serum nonprotein nitrogen which was 50 mg. per 100 cc. on entry, rose to 70 the first day, came down to 60 on the second, and to 30 on the seventh day. The plasma albumin was 3.2 grams per 100 cc. on the first day, 1.35 on the seventh day, and 3.1 on the 16th day. The total plasma protein levels on the same days were 5.3, 5.3, and 6.7. The metabolic and vitamin data are presented on Chart 3.

COMMENT: This relatively old, but muscular laborer had extremely severe injuries, with a long period of shock. The blood level of ascorbic acid and the urinary excretion of all four of his vitamins remained extremely low in comparison to his enormous intakes until the eighth day when they all increased to excretion levels which were normal for his intake.

CASE 5.—K. R., a 56-year-old white male, was admitted because of repeated hematemeses for 24 hours. The day before entry, while at work, he suddenly vomited a cupful of bright red blood. Shortly thereafter he felt some vague abdominal pain, dull in character. The pain began in the midlower abdomen and extended up to the xiphoid; it did not radiate. During the next 24 hours the patient had at least ten episodes of vomiting blood. After the first few he began to feel dizzy, weak, and somewhat sweaty. The abdominal pain disappeared gradually about 18 hours after onset.

Until one year ago the patient was in good health but during the past year he had noticed a gradual weight loss, possibly as much as 25 pounds, and loss of appetite. There has been no nausea, vomiting, abdominal pain, constipation, diarrhea, jaundice, light stools, or dark urine, or melena. He had had varicose veins for many years with occasional edema of the feet.

Physical examination revealed a well-developed man with some evidence of recent weight loss. He was apathetic and sweating. His temperature was 97°F. rectally; pulse 120, and blood pressure 78/65. The pulse was weak and thready and his extremities were cold. Abdominal examination revealed generalized spasm but no

tenderness. The upper border of liver dullness was in the sixth interspace on the right. The lower edge of the liver could not be felt, but by percussion, dullness was present four fingers below the costal margin. Peristalsis was absent. There were no distended veins or venules on the abdomen. No masses could be felt. Rectal examination was negative except for the presence of dark red and black colored fecal material. His skin was clear. There were no telangiectases or jaundice. There were no obvious bleeding points in the mouth or throat. The chest was emphysematous, resonant, with some coarse bronchial râles. The heart was not enlarged, and its sounds were of poor quality. Its rhythm was regular, and there were no murmurs. The extremities were negative except for marked varicosities bilaterally.

Laboratory data on entry revealed a red count of 2.7, hemoglobin of 62 per cent, icterus index 3, white count 12,000, and prothrombin 100 per cent of normal. His N.P.N. was 71 mg. per 100 cc., and his serum protein 4.5 grams per 100 cc. of serum. The stools showed a strongly positive guaiac test and the urine was negative except for moderate traces of albumin.

Clinical Course: During the first three hours, the patient was given two liters of blood and 1,800 cc. of intravenous saline. The blood pressure rose to 120/70, the pulse dropped to 84, and the temperature rose to 100.6°F. At this time, under spinal anesthesia supplemented by cyclopropane, a subtotal gastrectomy was done. No definite bleeding point was found. During this procedure the patient received an additional 300 cc. of blood. The pulse remained of good quality, about 80, and the blood pressure rose to 150/80. Postoperatively, the patient was put on gastric suction. The following day he was given intravenous protein hydrolysate and glucose which was continued daily for the next ten days. He was started on water and milk by mouth on the fifth day and a soft diet on the sixth day. The details of his caloric and nitrogen intake, and nitrogen output for the first two weeks are given in Table 4. He was in negative nitrogen balance during the first week, and then in slight positive nitrogen balance on the second week. Nitrogen balance studies were discontinued at this time. The patient lost 12 pounds of weight. The plasma protein concentration was above six.

On the 16th day he developed calf tenderness and a positive Homan's sign bilaterally. Therefore, a bilateral femoral ligation was performed. His temperature rose during the next four or five days to 102° and 103°F. Repeated blood cultures were negative except for one which was reported showing an *alpha* streptococcus. His temperature subsided slowly, but continued to rise to 100°F. each afternoon for about a week. His course thereafter was normal and he was discharged ten days later. The laboratory data are detailed in Tables IV and V and Chart 4.

COMMENT: During the first two weeks he received vitamin supplements only on the first, sixth, and 13th days as test doses for "low" saturation tests. During this time the fasting concentration of ascorbic acid varied between zero and 0.7 mg./100 cc. plasma. The values after "low" saturation tests on the first, sixth, and 13th days were very low, as indicated in Chart 4. The four-hour urine excretion of ascorbic acid during these saturation tests were also very low, particularly on the 13th day when only 13 mg. were excreted. The fasting hourly excretion of ascorbic acid was also low at the end of the second week. During this first two-week period, and in fact, the entire period study, the fasting hourly excretions and the response to tests for thiamin, riboflavin, and n-methyl-nicotinamide were within normal range.

During the third week a supplement of 225 mg. of ascorbic acid, 9 mg.

TABLE IV

CASE 5: K. R. HEMATEMESIS WITH SHOCK.

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Weight							143									137	133											131	
Temperature	97	104	103	103	100	100	100	100	103	101	100	101	101	101	100	100	102	103	103	103	102	101	101	100	100	101	100	100	99
Caloric intake	700	2600	1950	1900	3100	2900	2800	740	2350	2900	2100	1600																	
Nitrogen intake (grams)	11	14	12	12	18	22	10	7	22	26	16	17																	
Nitrogen output (grams)	11	9	18	18	24	23	16	16	23	23	15	16																	
Ascorbic acid intake (grams)	0	250	0	0	0	0	250	0	0	0	0	0	0	250	225	225	225	225	225	225	475	225	500	500	500	500	500	500	5,00
Plasma protein (grams per 100 cc.)					6.8							6.0																7.1	
Plasma ascorbic acid; (milligrams per 100 cc.)	0.3	0.0				0.5	0.0						0.8	0.0						0.2	0.0								0.8
Ascorbic acid output; (milligrams per hour)		1.2		2.1			1.3	2.5			0.8			0.7	0.4			1.2		1.3	3.1	2.1			2.1				4.3
Thiamin intake (milligrams per hour)		5					5							5	9	9	9	9	9	9	14	9	9	9	9	9	9	9	9
Thiamin output (micrograms per hour)	12		7				5	8			4			8	3			140		43	50	49			90				39
Riboflavin intake (milligrams per hour)		3					3							3	9	9	9	9	9	9	12	9	9	9	9	9	9	9	9
Riboflavin output (micrograms per hour)		40		70			65	1.8			1.0			54	52			184		150	300	85			250				75
Nicotinic acid intake; milligrams per hour)		50					50							50	75	75	75	75	75	75	125	75	75	75	75	75	75	75	75
N-methyl-nicotinamide output; (milligrams per hour)		0.6		0.5			0.5	0.3			0.2			0.4	0.2			0.5		0.4	1.0	0.5			1.3				0.5

each of thiamin and riboflavin, and 75 mg. of nicotinamide was given daily by mouth. The plasma ascorbic acid concentration both fasting, and after a "low" test on the 20th day, remained low as did the four-hour urinary excretion after injection of the test done.

CASE 6.—J. B., a 46-year-old white male, with a noncontributory past history, was admitted because of abdominal pain of 24 hours duration. He had been in good health until the day prior to entry, at which time he had sudden severe upper abdominal pain. Soon thereafter the pain reached to both shoulders, and he began vomiting, and vomited repeatedly until entry. There was no hematemesis or melena.

Examination revealed a fairly well-developed and well-nourished man who was dehydrated, apathetic, and in shock. His temperature was 97° F., and his pulse and blood pressure were unobtainable. The abdomen was spastic throughout, peristalsis was absent, and there was marked abdominal distention. The lung fields were clear.

TABLE V

CASE 5: K. R.—"LOW" SATURATION TESTS

	Excretion in Four Hours			
Day	Ascorbic Acid (Milligrams)	Thiamin (Milligrams)	Riboflavin (Milligrams)	N-methyl-nicotinamide (Milligrams)
1	24	0.8	0.9	7
6	21	1.2	0.4	9
13	13	1.3	0.9	11
20	50	1.7	1.1	8

The doses given were: Ascorbic acid, mg. 250; thiamin, mg. 5; riboflavin, mg. 3, and nicotinamide, mg. 50.

On entry, 1,500 cc. of saline were given intravenously within 40 minutes. The blood pressure rose to 100/65 and the pulse became of fairly good quality. An additional 3,000 cc. of saline were given in the next three and one-half hours; the blood pressure remaining between 92/60 and 108/90, and the pulse between 92 and 104. The temperature rose to 100.4°F. Whole blood was then started intravenously, 1,500 cc. being given in the next four hours. Thereafter he received a slow intravenous injection of 4 per cent Amigen and 15 per cent glucose.

Roentgenograms of the abdomen and chest revealed a large amount of free air under the right diaphragm, with some elevation of the right diaphragm and some clouding at the left lung base. Gastric drainage was started on entry. The abdominal distention increased gradually and led to marked impairment of the respiratory movements. An abdominal tap ten hours after entry yielded large amounts of gas and two liters plus of purulent yellowish-green fluid containing many gram-negative mobile rods. The respirations were much easier after the abdominal tap. The patient was placed in an oxygen tent and given penicillin, 20,000 units intravenously every two hours. The patient gradually became weaker, finally comatose, and died 36 hours after entry. The urine output had been low and during the last 24 hours he had intermittent periods of shock. The temperature rose to 103°F. An autopsy revealed an enormous opening in the stomach from a perforated ulcer.

Four hours after entry a saturation test was attempted. He was given ascorbic acid G 1.0, thiamin mg. 30, riboflavin mg. 12, and nicotinamide mg. 450. Unfortunately,

the urine output was negligible so that determination of vitamin outputs could not be made. The ascorbic acid plasma curve is shown in Chart 5.

COMMENT: A previously well, healthy male, with a neglected large perforation of a gastric ulcer, who entered the hospital in extreme shock. Although his blood pressure improved at times during treatment, he never reached a condition that seemed to warrant surgical intervention. His plasma ascorbic acid saturation curve showed a very low response to the test.

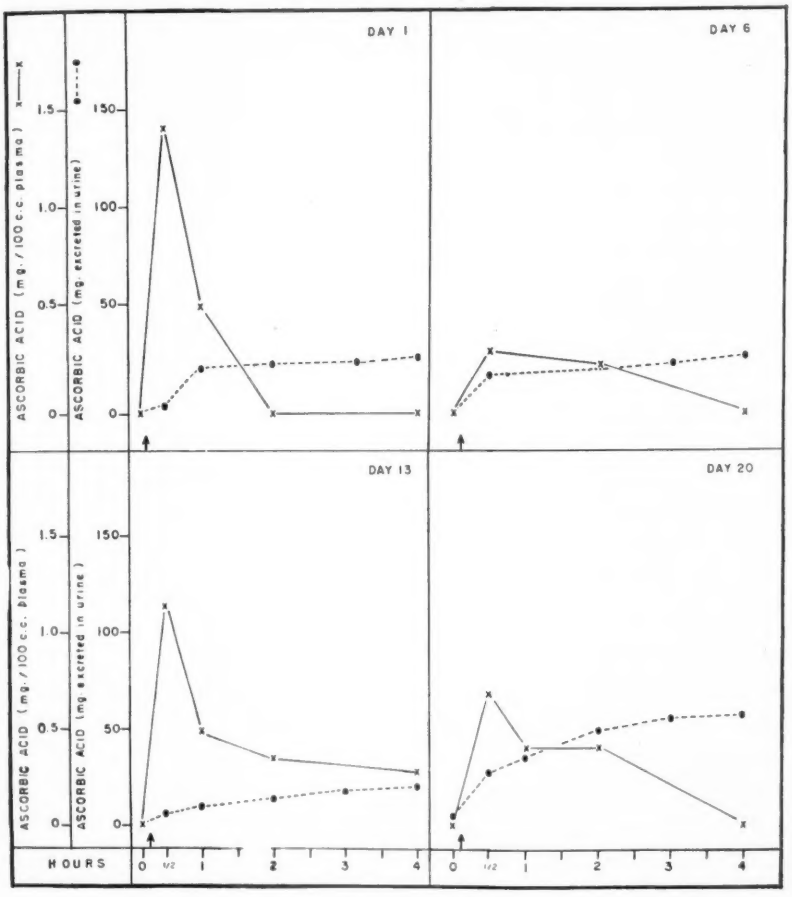


CHART IV

DISCUSSION.—The data presented demonstrate that six patients with severe injuries, hemorrhage, or infection had marked abnormalities in the metabolism of ascorbic acid, thiamin, riboflavin, and nicotinamide. These were evidenced by one or more of the following items: Low concentration of ascorbic acid in the plasma, fasting or after saturation tests, and low excretions of all four vitamins under the same two conditions. The abnormality is most marked when the patient is most sick; that is, when the metabolic

disturbances of the carbohydrates, proteins, and adrenocortical hormone are also most marked.

Theoretically, some or all of the findings might be accounted for by the following possibilities:

1. *Deficiencies before Injury.*—All of these patients had no recognizable signs or symptoms of deficiencies of these vitamins at the time of entry to the hospital. Several may have had less than fully saturated conditions of one or more of them. But the experiment of Crandon, Lund and Dill[10] showed that the plasma level fasting, and following therapy, and the excretion following therapy, rose much more rapidly after actual scurvy had been

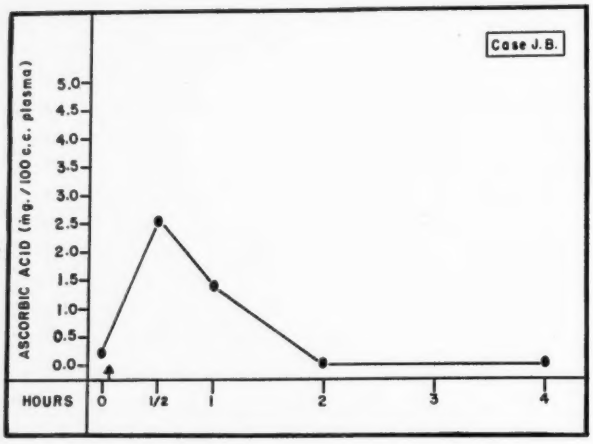


CHART V

treated with the same dose of ascorbic acid than these items rose in Patient 4 in this series. It does not seem possible that preëxisting deficiencies played any rôle in the findings in Patients 1, 2, 3, or 4 in this series, or more than a slight rôle in Cases 5 and 6.

2. *Inadequate Dosage.*—The dosage of vitamins administered varied from no dose to very large doses. Even the patients given the largest doses showed slight excretions during the acute phase of their illnesses but then showed very active excretions as soon as their metabolic disturbances were corrected.

3. *Failure of Absorption.*—Most of the vitamins were given intravenously. When they were given by mouth there were no instances of vomiting or diarrhea during the periods of mouth administration. Therefore, none of the results could have resulted from lack of opportunity for the vitamins to enter the blood.

4. *Excretion in the Sweat.*—That deficiencies might result from losses in the sweat has been postulated. Sargent, Robinson, and Johnson[11] have recently shown that sweating cannot cause important losses of these vitamins.

5. *Secretion in Exudates.*—Vitamins might be lost into exudates. Only one of the six patients (Case 6) had any important exudates.

6. *Storage.*—As noted in the introduction, Andreae, and his associates, interpret the evidence from their study of riboflavin excretion after injury as showing that riboflavin is stored early and excreted later. There is no data in the present study that confirms this finding for riboflavin. However, this difference in findings may be the result of differences in the technic of study. Andreae used the balance technic rather than the "fasting hour." At the same time, there is no evidence that any of the other vitamins react in this way.

7. *Destruction.*—It is possible that vitamins may be destroyed without performing any useful function during their destruction. This study contributes no evidence for or against such a postulate.

8. *Increased Utilization.*—Holt[12] has shown increased utilization of thiamin in conditions of stress such as increased basal metabolism and fever. As mentioned above, other stresses associated with acute hemorrhage or other medical or surgical illness, are followed by markedly increased turnover of protein and carbohydrate. Since the vitamins of the B group discussed here are intimately concerned with the metabolism of these substances, it is likely that the demand for, and utilization of them is increased. Similarly, it has been postulated that the demand for and utilization of ascorbic acid is increased due to its relation to the adrenocortical hormones.[2] The findings in the present study can best be explained by increased utilization.

It may be asked whether there is evidence in this study that administration of these vitamins was beneficial to these patients. Such evidence could only result from the study of large numbers of cases with comparable injuries or disease. Even the patients whose recovery was particularly gratifying (Cases 2, 4, and for the first eight days Case 3) and who were given large doses of vitamins had so many other powerful therapeutic agents used that we can have no opinion in answer to this question. On the other hand, the experimental work quoted above, and the demonstration of actual or apparent deficiency of ascorbic acid in the plasma and of all four vitamins in the urine under the conditions of the study, indicate that such treatment is reasonable as an attempt to aid the organism to achieve homeostasis.

If one accepts the possibility that these vitamins are useful in these conditions, do these results indicate any particular doses for such cases? It would seem reasonable to use doses of not less than one gram of ascorbic acid, 50 mg. of thiamin, 50 mg. or riboflavin, and 500 mg. of nicotinic acid per day during the period of acute stress and for two or three days afterward. Such doses will not result in any wastage of vitamins by excessive urinary secretion if they are given to patients with illness or injuries comparable to those of the patients studied. After this early period, the doses might well be reduced to 200 mg. ascorbic acid, 10 mg. of thiamin, 10 mg. of riboflavin, and 75 mg. of nicotinic acid until convalescence is well-established. This

study has not been carried into later convalescence so no estimate of the needs at that time can be given.

SUMMARY

1. Six patients with severe acute surgical conditions have been studied with respect to the plasma level of ascorbic acid and the excretion of ascorbic acid, thiamin, riboflavin, and nicotinic acid.

2. Abnormally small amounts of one or more of these substances have been found in many specimens from all cases during the period of the acute illness.

3. This study gives some further support to the idea that large doses of ascorbic acid, thiamin, riboflavin, and nicotinic acid may serve a useful purpose in the care of acutely ill people.

REFERENCES

1 Govier, W. M.: Rationale for Use of Vitamins in the Therapy of Shock and Anoxia. J. A. M. A., **126**, 749–750, November 18, 1944.

2 Sayers, G., Sayers, M. A., Liang, T.-Y., and Long, C. N. H.: The Effect of Pituitary Adrenotropic Hormone on the Cholesterol and Ascorbic Acid Content of the Adrenal of the Rat and the Guinea-pig. Endocrinology, **38**, 1–9, January, 1946.

3 Uzbekov, G. A.: Problems of Avitaminosis: Effect of Burns on the Metabolism of Vitamin C. Klin. Med., **15**, 237–240, 1937.

4 Clark, E. J., and Rossiter, R. J.: Carbohydrate Metabolism after Burning. Quart. Jl. Exper. Physiol., **32**, 279–300, 1944.

5 Andreae, W. A., Schenker, V., and Browne, J. S. L.: Riboflavin Metabolism after Trauma and during Convalescence in Man. Federation Proceedings, **5**, 3, 1946.

6 Levenson, S. M., Davidson, C. S., Lund, C. C., and Taylor, F. H. L.: The Nutrition of Patients with Thermal Burns. Surg., Gynec., and Obst., **80**, 449–469, May, 1945.

7 Mindlin, R. L., and Butler, A. M.: Determination of Ascorbic Acid in Plasma: Macromethod and Micromethod. J. Biol. Chem., **122**, 673–686, 1938.

8 Johnson, R. E., Sargent, F., Robinson, P. F., and Consolazio, F. C.: Assessment of Nutritional and Metabolic Conditions in the Field. War Medicine, **7**, 227–233, 1945.

9 Lewis, J., Davidson, C. S., Johnson, R. E., and Taylor, F. H. L.: The Response of Normal Subjects to "High" and "Low" Saturation Tests for Ascorbic Acid, Thiamin, Riboflavin and Nicotinic Acid. In preparation.

10 Crandon, J. H., Lund, C. C., and Dill, D. B.: Experimental Human Scurvy. N. E. Jour. of Med., **223**, 353–369, 1940.

11 Sargent, F., Robinson, P., and Johnson, R. E.: Water Soluble Vitamins in Sweat. J. Biol. Chem., **153**, 285–294, 1944.

12 Holt, L. E., Jr.: The Thiamin Requirement of Man. Federation Proceedings, **3**, 171–178, September, 1944.

THE TREATMENT OF ACUTE RENAL FAILURE BY PERITONEAL IRRIGATION*

JACOB FINE, M.D., HOWARD A. FRANK, M.D., AND ARNOLD M. SELIGMAN, M.D.

BOSTON, MASSACHUSETTS

FROM THE SURGICAL RESEARCH DEPARTMENT, BETH ISRAEL HOSPITAL, BOSTON, AND THE DEPARTMENT OF SURGERY, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

CERTAIN TYPES of acute renal failure need not be fatal if the period necessary for repair can be provided by utilizing an extrarenal pathway as a temporary substitute for the normal excretory function of the kidney. We have already published the experimental data[1] and one clinical experience[2] demonstrating the possibilities of continuous peritoneal irrigation for this purpose.

The peritoneal membrane has long been recognized to be an excellent dialyzing membrane, readily permeable to water and crystalloids.[3] Peritoneal irrigation makes use of this dialyzing capacity for the removal of diffusible substances from the plasma and ultimately from the extracellular fluid. Proper adjustment of the composition of the irrigating fluid prevents the depletion below normal concentration of the plasma of its normal constituents and thereby protects the chemical structure of the extracellular fluids.

We have referred elsewhere[1] to efforts by others† to utilize the peritoneum. In an experimental study in dogs[1] it was found that adequately conducted peritoneal irrigation would provide 40–75 per cent of normal kidney function in terms of urea clearance, correct acidosis, and prevent death from uremia following bilateral nephrectomy. In the present report our clinical experience with this method will be discussed.

METHOD

The irrigation fluid is modified Tyrode's solution containing the following amounts of anhydrous substances per liter: NaCl 8.0 grams, KCl 0.2 gram, $CaCl_2$ 0.1 gram, $MgCl_2$ 0.1 gram, NaH_2PO_4 0.05 gram, $NaHCO_3$ 1.0 gram, and dextrose 1.5 grams. It is prepared in large volume as follows: Fifteen liters of freshly distilled sterile water are run into a sterile 20-liter pyrex carboy. With the exception of sodium bicarbonate all the salts and the glucose for 18 liters of irrigating fluid are dissolved in two liters of distilled

* Part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

† Additional references: Bliss, S., Kastler, A. O., and Nadler, S. B., Proc. Soc. Exp. Biol. and Med., 29, 1078, 1932; Haam, E. V. and Fine, A., Pros. Soc. Exp. Biol. and Med., 30, 396, 1932; Rhoads, J. E., Am. J. Med. Sci., 196, 642, 1938; Wear, J. B., Sisk, I. R., and Trinkle, A. J., J. Urol., 39, 53, 1938; Abbott, W. B. and Shea, P., Am. J. Med. Sci., 211, 312, 1946.

Read before the American Surgical Association, April 2–4, 1946, Hot Springs, Virginia.

water and autoclaved. The $NaHCO_3$ for 18 liters is dissolved and autoclaved separately in a liter of distilled water. *It is important not to heat the bicarbonate solution with the other salts and glucose because of precipitation of calcium and magnesium salts and the production from glucose of toxic substances (probably aldehydes), which may be fatal.* Sterile solutions in small volume of the sodium salt of heparin (0.25–0.50 mg. per liter), of penicillin (2,500–5,000 units per liter) and of sulfadiazine (60–120 mg. per liter) together with the solutions of the salts and glucose are added to the water in the carboy at room temperature. Heparin is used to prevent the formation of fibrin and intestinal adhesions. Penicillin is used for prophylaxis against infection. Sodium sulfadiazine should not be added if renal sensitivity to sulfonamides is present or suspected.

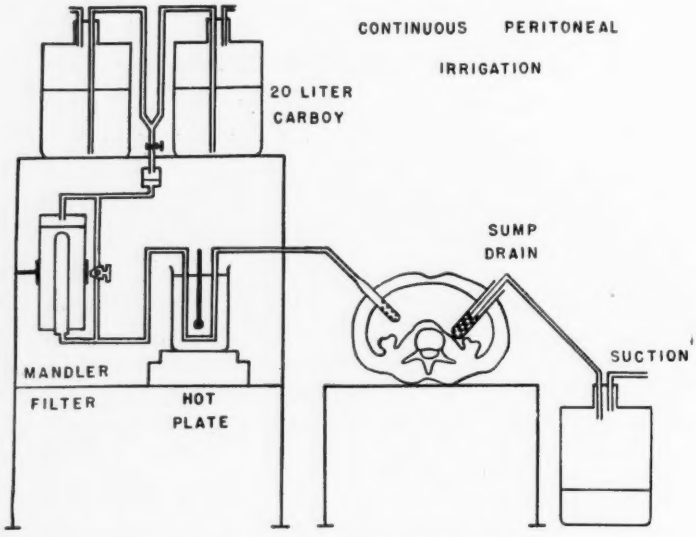


FIG. 1.—Diagrammatic representation of the circuit for continuous peritoneal irrigation.

Occasional modifications in the composition of the fluid were made, as indicated in the case reports. Further changes may be indicated as more experience is acquired. Since edema of the peritoneal membrane does not occur in consequence of irrigation, protein is not used as a rule. When protein seems indicated (as in Case 4), gelatin is used, since the large amount of protein required makes the use of human albumin impracticable, though probably preferable. If gelatin solution, which is acid in reaction, is used it should be brought to pH 7.5 with concentrated NaOH.

The fluid flows by gravity from two elevated carboys through siphon tubes, joined by a Y-tube, through a drip-bulb, then either directly or preferably through a Mandler (Berkefeld) filter to a glass U-tube in a water bath (40°C.–45°C.) and thence to the peritoneal inlet-tube (Fig. 1). The filter candle is eight inches long and one inch in diameter and permits a flow

of 40–60 cc./min. of a protein-free solution when the carboys are elevated two to three feet above the bed, as indicated in the photograph (Fig. 2). The inlet tube is a rubber catheter or a perforated small stainless steel tube. The outlet tube used in earlier cases was a whistle-tip catheter or a large-bore mushroom-tip catheter connected to a receiving carboy on the floor. The outlet tube proved unsatisfactory because of frequent plugging. Accordingly, in later cases a stainless steel sump-drain (Figs. 1 and 3), which is similar to the metal-perforated suction tube commonly available in operating rooms, was used as an outflow tube attached to a constant suction line. This has

FIG. 2.—Photograph of apparatus for peritoneal irrigation.

proved entirely satisfactory and remains patent indefinitely. The inflow and the outflow tubes are inserted under local anesthesia into the peritoneal cavity, through small incisions, one in each flank. The sump-drain is directed into the cul-de-sac.

Collateral therapy, referred to in the case reports, is necessary for maintaining nutrition and water-soluble vitamin balance, correcting anemia, acidosis, hypoproteinemia and for the treatment of associated disease.

CASE REPORTS

CASE 1.—B.I.H. No. 82847: I. E., female, age 49, was transferred to us from another hospital because of uremia caused by ureteral obstruction due to recurrent carcinoma of the cervix. She had entered the other hospital complaining of headache, anorexia, nausea, vomiting, and weight loss. Examination at that time showed her to be alert and coöperative. She was afebrile. She had purpuric spots on the arms

FIG. 3-A

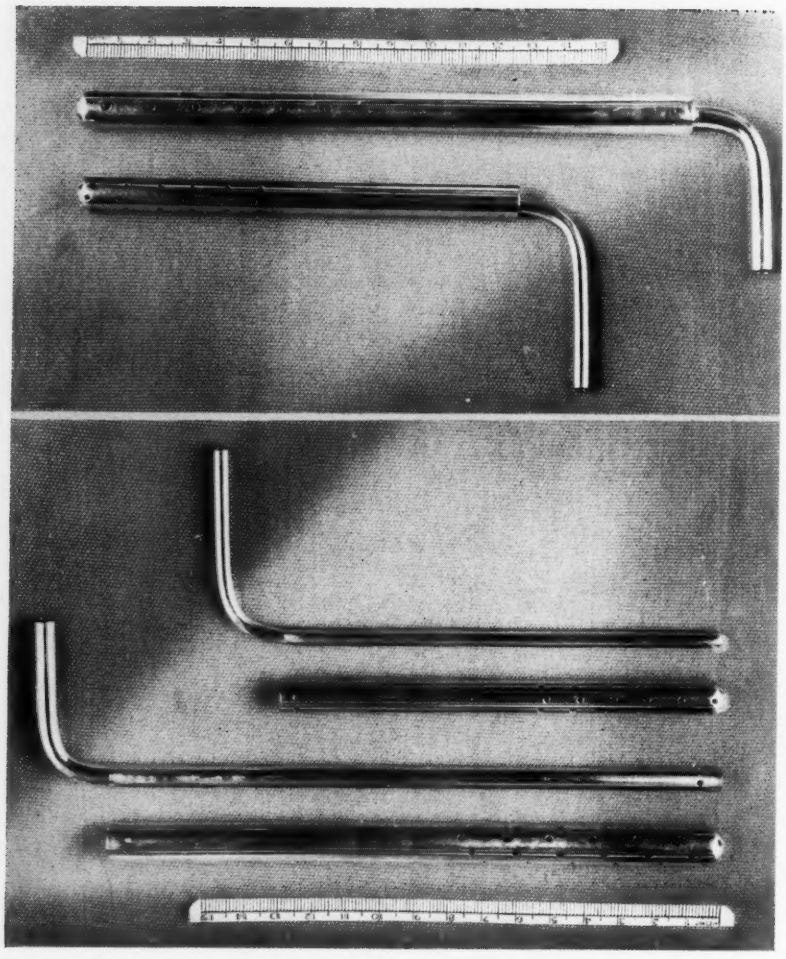


FIG. 3-B

FIG. 3-A and FIG. 3-B.—Sump-drain.

and legs and multiple fresh hemorrhages in the optic fundi. The blood pressure was 230/120. The apex of the vagina was fixed in a hard irregular tumor mass which extended laterally to fill the pelvis. The urine contained 2+ albumin and occasional white and red cells. The hemoglobin was 100 per cent. The blood N.P.N. was 105 mg. per cent, the blood urea N 83 mg. per cent. At cystoscopy, no excretion of phenolsulfonphthalein was observed from the left ureter and only 2 per cent from the right ureter in ten minutes. Catheters reached the kidneys through tortuous ureters. Retrograde pyelograms showed dilatation of both renal pelves.

Nausea and vomiting necessitated parenteral alimentation. In spite of an adequate fluid intake, the total urine output was 10 to 40 cc. per 24 hours in each of the last four days prior to transfer to this hospital. Headache increased and mental alertness diminished. A pericardial friction rub appeared. She showed generalized edema. The patient's condition and prognosis were too poor to warrant nephrostomy or ureterostomy.

Upon transfer to this hospital two mushroom catheters were placed in the peri-

TABLE I

CASE 1. BLOOD UREA CLEARANCE* BY PERITONEAL IRRIGATION TESTED FOR SHORT PERIODS AT VARYING RATES OF FLOW

Flow Rate Cc./Min.	Peritoneal Fluid Urea N Conc. Mg. %	Blood Urea Clearance Cc./Min.
19	50.4	11.2
47	32.1	14.5
58	23.9	15.6
66	13.8	9.7
83	13.0	11.7
127	11.1	14.3

* Blood urea clearance by peritoneal route was calculated in the same way as urinary urea clearance using peritoneal fluid rate of flow and urea concentration in place of urinary values.

toneal cavity, which contained a large volume of free fluid (0 day, Fig. 4). The following day, when the blood N.P.N. was 195 mg. per cent, irrigation was started. Test periods of irrigation, with one-half hour intervals in between, at rates of flow varying from 19 cc./min. to 127 cc./min. indicated a maximum clearance of blood urea when the flow rate varied 40–60 cc./min. (Table I).

The next day continuous irrigation was carried out at a rate of 45 cc./min. for 24 hours. In this period 23 grams of urea were removed and an average blood urea clearance value of 16 cc./min. was attained. After an interval of four hours irrigation was resumed for another 24 hours, this time at an average rate of 60 cc./min. In this period 24 grams of urea were removed and the blood urea clearance value was 23

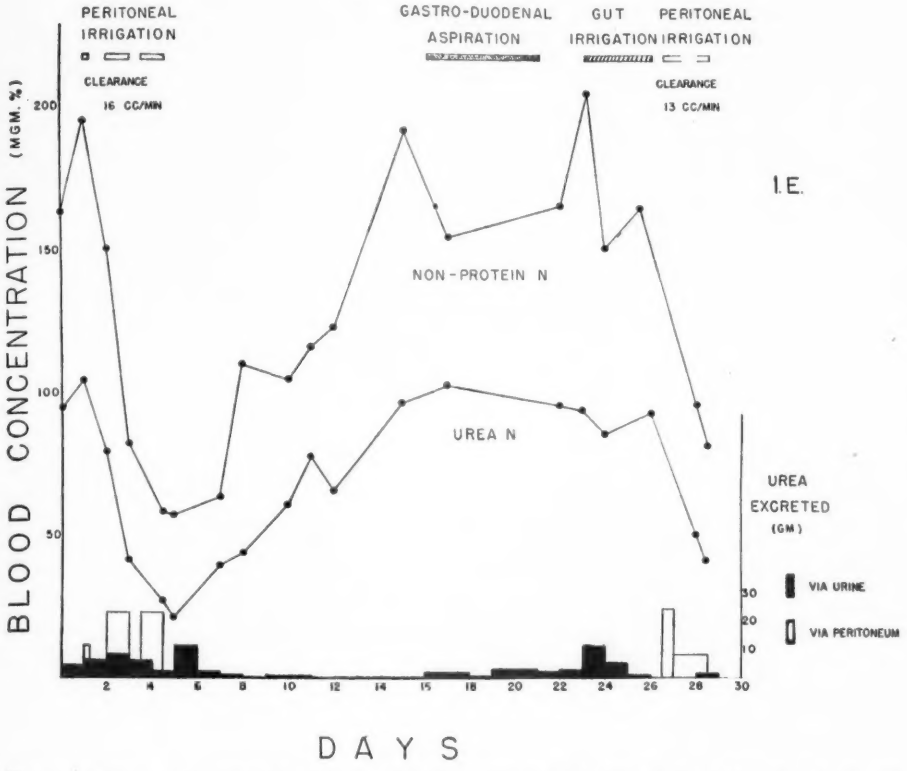


FIG. 4.—Case 1: Course of azotemia and daily urea elimination by the kidneys and by the peritoneum.

cc./min. After these two and one-half days of intermittent peritoneal irrigation, the blood N.P.N. concentration was 57 mg. per cent and the blood urea N was 21 mg. per cent. The patient was relieved entirely of headache, anorexia, nausea, and vomiting, and was alert. The blood pressure remained unchanged Transfusions were given to correct anemia. The irrigation produced no discomfort and the tubes required only occasional attention when the outflow catheter blocked.

During the period of peritoneal irrigation the volume of urine excreted increased up to 1,400 cc. per day. However the urea N content of the urine did not exceed 400 mg. per cent and total daily urinary urea excretion did not exceed ten grams. In view of the correction of the uremia and the apparent return of urine flow, peritoneal irrigation was discontinued.

Urinary output fell again and the clinical and chemical evidence of uremia gradually returned. Both peritoneal catheters were blocked. Nausea and vomiting recurred. A Miller-Abbott tube was passed and gastroduodenal suction instituted. The fluid removed was replaced by physiologic saline given intravenously. When the volume of aspirated fluid was less than 500 cc. per day its urea N content reached 64 mg. per cent, but when over 3,000 cc. per day was aspirated its urea N content was only 15 mg. per cent. Not more than one gram of urea per 24 hours was obtained by gastroduodenal aspiration. The uremic state was not improved.

Under spinal anesthesia an isolated 12-inch loop of ileum, with both ends exteriorized, was constructed in order to determine whether irrigation of the intestine in man would function adequately when peritoneal irrigation was impossible for one reason or another. Scattered omental and peritoneal metastases were found and histologic examination of one nodule disclosed undifferentiated carcinoma. No evidence of peritoneal inflammation from the preceding irrigation was found. The ends of the peritoneal catheters were firmly encased in omentum. Irrigation through the loop of

TABLE II

CASE 1: BLOOD UREA CLEARANCE BY IRRIGATION OF ILEAL LOOP TESTED FOR SHORT PERIODS AT VARYING RATES OF FLOW

Flow Rate Cc./Min.	Irrigation Fluid Urea N Conc. Mg. %	Urea Clearance Via Intestine Cc./Min.	Urea Clearance Via Intestine Cc./Min./In. Intestine Length
7.8	7.0	0.6	0.5
14.6	3.3	0.54	
15.5	2.9	0.48	.04
15.8	3.0	0.52	
32.2	1.4	0.52	
46.0	0.7	0.36	.03
63.0	0.5	0.34	
166.6	0.2	0.31	

ileum for short test periods at various rates showed so poor a clearance of blood urea (Table II) as to indicate that perfusion of a loop 200 inches long would be required to achieve a blood urea clearance of 10 cc. per minute, a rate which is approximately the minimum clearance necessary to avoid the development of uremia.[4] In the next three days, during which postoperative convalescence was entirely satisfactory, continuous irrigation through the loop at a rate of about 15 cc./min. was performed. The average urea clearance value per 24 hours was 0.56 cc./min. and the total amount of urea removed in the 24-hour period was only 0.1 Gm. (Fifty per cent magnesium sulfate irrigated through the loop was ineffective in increasing fluid and urea output and produced nausea and vomiting.) The blood urea N level was not improved and the patient's clinical condition became steadily worse. She lapsed into uremia and seemed moribund.

Two straight catheters were then introduced into the peritoneal cavity, under local anesthesia. They were passed with the aid of a stylet alongside the emerging

ends of the isolated loop of intestine. In the subsequent 24 hours, 38 liters of fluid were irrigated through the peritoneal cavity and 30 liters in the following 36 hours. An average blood urea clearance value of 13 cc./min. was attained and 35 Gm. of urea removed, with resulting satisfactory reduction in blood levels of N.P.N. and urea N. Clinical evidence of uremia disappeared. Irrigation was discontinued at this time.

Thereafter nothing was done to prevent the recurrence of uremia, steadily progressive anemia and malnutrition. The patient was kept comfortable by symptomatic therapy. She died a month and a half after irrigation therapy was ended. During this terminal period she excreted up to 1,000 cc. of urine daily and the progression of the uremic state was very slow.

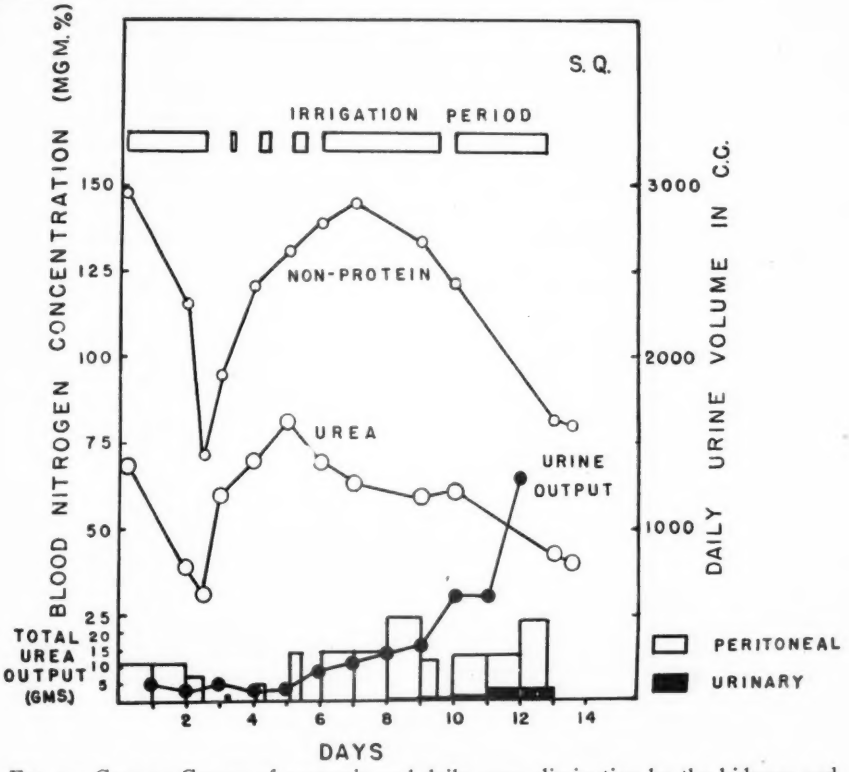


FIG. 5.—Case 2: Course of azotemia and daily urea elimination by the kidneys and by the peritoneum.

Autopsy showed the pelvis filled with carcinoma and scattered metastases in omentum and liver. The lower ureters were narrowed by tumor tissue so that there was considerable difficulty in forcing urine through them. The upper ureters were dilated. The kidneys were small and had dilated pelves and calices, surrounded by a narrowed rim of cortex. Microscopically they showed only edema and tubular degeneration. There was no evidence of peritonitis.

COMMENT: This case was our first clinical trial of continuous irrigation for uremia. It was learned that continuous peritoneal irrigation can be carried out without discomfort to the patient and without the production of peritonitis. An optimal rate of irrigation was determined and shown to be capable of rapidly reducing the blood levels of nitrogenous substances to normal with simultaneous correction of the uremic state.

It was learned further that irrigation of the intestine, which would have advantages over peritoneal irrigation if effective, is not a satisfactory substitute.

CASE 2.—B. I. H. No. 83789: S. Q., a 14-year-old girl, entered another hospital because of repeated nose bleeds of one month's duration. She was found to have a low grade fever, mycrocytic, hypochromic anemia, a loud systolic apical murmur, left axis deviation and an elevated sedimentation rate. The diagnosis of active rheumatic fever was made. She was given ferrous sulphate and 100 grains of aspirin daily. After five days of salicylate therapy, nausea, vomiting, marked hyperventilation and stupor were noted. The blood pH was 7.45 and CO_2 combining capacity was 20 volumes per cent. These findings were attributed to salicylate poisoning which is said to produce a primary respiratory alkalosis from central stimulation,[5] with a compensatory fall in alkali reserve. She was given 10 per cent CO_2 inhalations, morphine, 1.2 grams of ammonium chloride, 4,500 cc. of glucose in saline and 500 cc. of blood, later found to be incompatible. Seven hours after the transfusion she showed hemoglobinemia and hemo-

TABLE III

CASE 2: DAILY EXCRETION OF UREA BY PERITONEAL IRRIGATION AND BY THE KIDNEYS

	Peritoneal Fluid				Urine				Blood	Blood Urea Clearance (Cc./Min.)	
Days*	Volume Cc.	Flow Rate Cc./Min.	Urea N Mg. %	Total Urea Gm.	Volume Cc.	Flow Rate Cc./Min.	Urea N Mg. %	Total Urea Gm.	Urea N Mg. %	Peritoneal	Renal
0	9250	6.0	61	11.3	0	—	—	—	68	5.4	
1	9250	6.0	61	11.3	108	.08	20	.04	55	6.7	
2	9000	12.5	38	6.8	64	.05	15	.02	35	13.5	
3	2000	11.0	56	2.2	109	.08	60	.13	60	10.3	
4	3000	8.0	76	4.6	60	.04	40	.05	70	8.7	
5	9000	16.6	77	13.9	74	.05	74	.11	82	15.6	
6	18000	12.5	39	14.0	184	.13	40	.15	68	7.2	
7	18000	12.5	39	14.0	210	.15	109	.46	63	7.7	0.25
8	24000	16.6	50	24.0	260	.18	89	.46	60	13.8	0.27
9	12000	16.6	50	12.0	305	.21	122	.75	60	13.8	0.43
10	18000	12.5	37	13.3	610	.43	78	.95	62	7.5	0.54
11	18000	12.5	37	13.3	610	.43	260	3.00	55	8.4	2.01
12	36000	40.0	32	23.0	1300	.88	118	3.10	45	28.5	2.40

* From the start of irrigation; numbers correspond with days indicated in Fig. 5.

globinuria. The pH of the urine was 4.5. She was given sodium bicarbonate and sodium lactate. The temperature rose to 103° F. In the subsequent two days she voided no more than 30 cc. of urine per day. She remained hyperpneic and stuporous, with a blood CO_2 combining capacity at or below 30 volumes per cent. Diathermy to the kidney areas failed to increase urine output.

The patient was transferred to us 48 hours after the hemolytic reaction was recognized. On admission, she was pale, edematous and stuporous. She coughed frequently. There were diminished breath sounds and râles at both lung bases. The heart was enlarged, with a loud apical systolic murmur and thrill. Pulse rate was 110. The rectal temperature was 100.6° F., and the respiratory rate 30 per minute. The urine was clear and straw-colored, alkaline, sp. gr. 1.010, albumin 4+, 15–20 W.B.C. and R.B.C. The red cell count was 2.45 millions and the Hb 36 per cent. The blood N.P.N. was 78 mg. per cent. Chest roentgenograms showed mitral valvular disease, consolidation of both lower lobes, and questionable left pleural effusion.

In view of the brief duration of the anuria and the complicating illnesses, uremia was not considered the immediate primary problem. Accordingly, peritoneal irrigation was deferred for 36 hours. During this time she was given 1,000 cc. of blood in two transfusions, glucose in distilled water in small volume, parenteral penicillin (100,000

units per 24 hours) and sodium sulfadiazine (2.5 Gm. per 24 hours). Mental clarity improved and temperature and pulse returned to normal. The total urine output in this period was less than 30 cc.

Without removing the patient from bed, two whistle-tip rubber catheters were introduced, under local anesthesia, into the peritoneal cavity and irrigation was begun. Figure 5 and Table III indicate the effect of the irrigation in terms of total urea removed, changes in blood level of nonprotein and urea nitrogen and calculated urea clearance. In the early period flow rates considerably slower than optimal were used because recurring difficulty with the outflow tube led to recurring distention of the peritoneal cavity with fluid. Repeated adjustments of the outlet tube were necessary. In spite of this, significant blood urea clearance was achieved, blood nitrogen levels were markedly improved, the blood CO_2 combining capacity rose to 48 volumes per cent, and alertness returned. Nevertheless, she remained sick, exhibiting a low-grade swinging fever, evidence of congestive heart failure, pneumonia, and episodes of paroxysmal dyspnea, cyanosis and tachycardia. Gastric distention required suction drainage. The hemoglobin level was restored to 80 per cent by transfusion. She was fully digitalized and penicillin and sulfadiazine therapy were continued. Since she was no longer uremic and since the avoidance of abdominal distention was desired, peritoneal irrigation was almost completely discontinued for two days, during which the clinical and chemical evidence of uremia recurred. The CO_2 combining capacity dropped to 24 volumes per cent.

Accordingly, two large-bore mushroom-tip rubber catheters, instead of whistle-tip catheters previously used, were implanted in the peritoneal cavity through small lateral abdominal incisions made, under local anesthesia. No evidence of peritonitis was seen. Irrigation through these tubes proceeded satisfactorily although blockage of outflow did recur from time to time. The uremic state was corrected. During this period, ileus required almost continuous Miller-Abbott tube therapy. The peritoneal outflow fluid in the subsequent week remained sterile. On the last day of irrigation the colon bacillus was found in the outflow fluid. In spite of a complexity of confusing symptomatology chiefly referrable to the cardiorespiratory system, the general trend of the clinical condition was one of gradual improvement and all evidence of uremia eventually disappeared.

Meanwhile, there was evidence of recovery of renal function. On the second day of irrigation, 5.5 days after the transfusion reaction, 108 cc. of urine were excreted. On each of the subsequent four days from 60 to 110 cc. of urine were excreted. The urea content of this urine was less than 75 mg. per cent, so that the total urinary excretion of nitrogen was negligible and uremia recurred when peritoneal irrigation was interrupted. On the sixth day of irrigation the urine volume increased to 184 cc. and continued to increase thereafter until it reached 1,300 cc. on the 12th day of irrigation, or 15.5 days after renal shutdown. The urinary urea excretion, however, did not keep pace with the recovery of volume output and was still insufficient to prevent recurrence of uremia. Since improvement in kidney function seemed to be progressive, irrigation was temporarily discontinued. On the next day (16th day) when she seemed very much better and indeed apparently convalescing, she suddenly died, following a severe paroxysm of dyspnea. Postmortem examination disclosed multiple small pulmonary emboli, the sources of which were mural thrombi in the right ventricle and auricle. There was a minimal amount of rhemuatic heart disease and vegetative endocarditis. There was no peritoneal reaction of consequence at the site of the catheters but 100 cc. of turbid fluid containing the colon bacillus was found in the pelvis, which also showed a low grade inflammation with delicate, fibrinous adhesions between loops of intestine. The kidneys were swollen and pale except for congested pyramids. Microscopically, they showed a few brown granular hemoglobin casts in the tubules. Most of the tubules were dilated and lined with flattened regenerated epithelium.

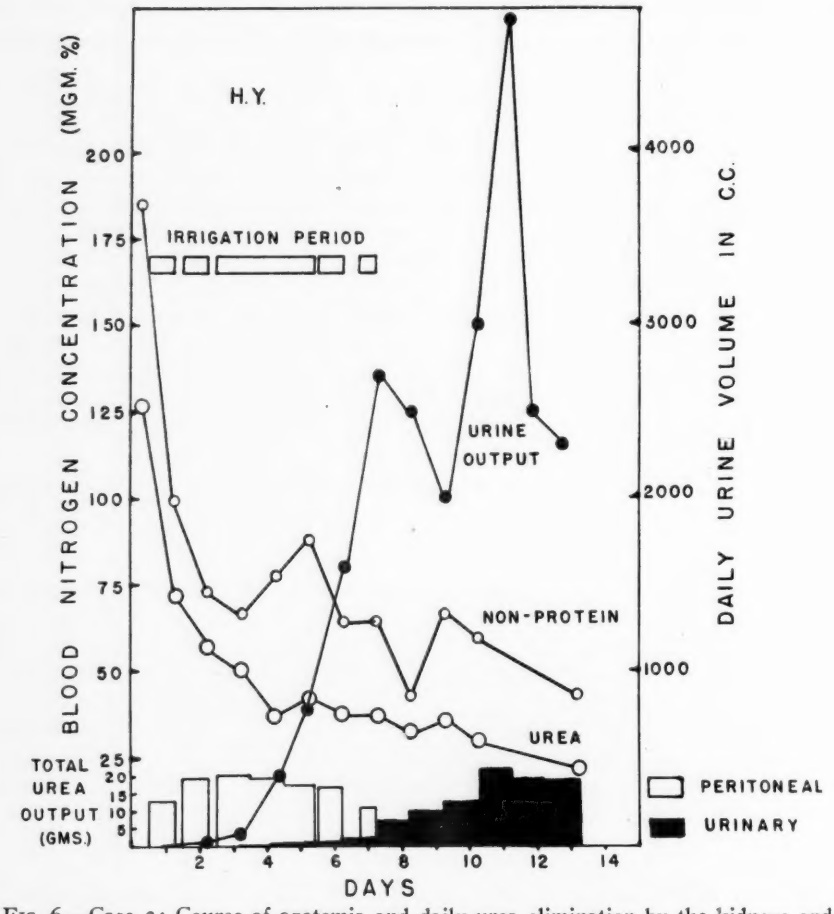


FIG. 6.—Case 3: Course of azotemia and daily urea elimination by the kidneys and by the peritoneum.

COMMENT: The immediate cause of death was multiple pulmonary emboli. In spite of the multiplicity of grave disorders complicating the acute renal shutdown, peritoneal irrigation achieved the purpose of eliminating the uremic state except during the period when the first set of catheters stopped working well. Renal shutdown was virtually complete for 13 days after the incompatible transfusion, at which time significant diuresis began (over 500 cc. per day) and the urinary urea output was increasing so that recovery sufficient to maintain electrolyte equilibrium might have been expected shortly. Although the recovery of function after renal shutdown from an incompatible transfusion begins, as a rule, at about this time, it is possible that elimination of the uremic state relieves the kidney, as it presumably must all other tissues, of an added burden which itself may prolong the recovery period. Peritoneal irrigation, therefore, may serve not only to delay death until renal recovery takes place but may also shorten the period necessary for recovery.

The colon bacillus infection of the peritoneum appeared on the 12th day of irrigation. Its extent and severity did not seem to contribute significantly to the lethal outcome.

It was clear from this experience that a catheter would not do as an outflow tube — so that in the next patient a stainless steel sump-drain was used instead. This functioned with complete satisfaction.

CASE 3.—B. I. H. No. 85197: H. Y. This case has been reported fully elsewhere.[2] A summary of the pertinent data follows: A man, age 51, developed anuria five days before admission to the hospital after 14 days of sulfathiazole therapy for an acute infection. After admission to the hospital, excessive parenteral fluids produced generalized edema and uremic intoxication became extreme. A study of the urinary tract disclosed parenchymatous renal damage. After five more days of anuria, at a time when the patient seemed moribund, peritoneal irrigation was started (0 day, Fig. 6 and Table IV). In spite of severe ileus, pulmonary edema and acidosis, the azotemia was reduced to near normal values within 48 to 72 hours. On the fourth day of irrigation, after 14 days of virtually complete anuria, urine output began and increased steadily thereafter. The urinary urea excretion reached a level capable of

TABLE IV

CASE 3: DAILY EXCRETION OF UREA BY PERITONEAL IRRIGATION AND BY THE KIDNEYS

	Peritoneal Fluid			Urine			Blood
Days*	Flow Rate Cc./Min.	Urea N Conc. Mg. %	Blood Urea Clearance Cc./Min.	Flow Rate Cc./Min.	Urea N Conc. Mg. %	Blood Urea Clearance Cc./Min.	Urea N Conc. Mg. %
1	25	24.4	8.4	—	—	—	72.7
2	33	27.4	14.5	0.02	85.0	0.03	62.2
3	25	28.1	13.8	0.04	66.0	0.05	50.6
4	25	26.0	17.2	0.28	75.0	0.55	37.8
5	13	31.2	9.5	0.55	50.0	0.65	42.8
6	35	21.0	19.4	1.10	62.5	1.82	37.8
7	29	26.5	21.0	1.87	32.5	1.65	36.7
8				1.74	145.0	7.60	33.3
9				1.40	255.0	9.70	36.8
10				2.30	193.0	14.80	30.0
11				3.30	225.0	24.70	
12				1.74	370.0	26.00	
13				1.60	392.0	28.50	22.0

* From the start of peritoneal irrigation; numbers correspond with days indicated in Figure 6.

preventing uremia on the seventh day of irrigation. At this time the irrigation was stopped. Progressive improvement in renal function continued thereafter and the patient left the hospital quite fit one week later, at which time renal function, in terms of urea clearance, was 33 per cent of normal. One month later renal function, in terms of urea clearance, was 50 per cent of normal and the P.S.P. test was normal. A year later kidney function was no better.

Pulmonary edema was considerable and distressing on the third day of irrigation. All parenteral fluids were omitted from then on. Glucose was added to the peritoneal fluid to correct starvation acidosis. At the same time troublesome ileus required tube suction, which yielded 6,000 cc. of fluid on the third and fourth days. The edema rapidly cleared thereafter. On the third day of irrigation, *E. coli* appeared in the outflow liquid, but there was no other clinical evidence of peritonitis even though this organism and leukocytes persisted until irrigation was stopped. On the first and second days after irrigation was discontinued, one million units of streptomycin in a liter of saline was injected intraperitoneally even though the patient seemed not to require chemotherapy.

COMMENT: Parenchymatous damage to the kidney from sulfathiazole is usually fatal. This patient was almost moribund when peritoneal irrigation was started. A cure seems to have been achieved in this patient by this method.

CASE 4.—C. W., a 19-year-old girl, entered another hospital for the surgical correction of cardiospasm. An esophagoplasty was done through the left chest. During the operation she received 500 cc. of Type-A blood (Rh positive). The patient's blood group was thought to have been Type A but later investigation demonstrated her to be Type-O (Rh positive). The patient's preoperative blood pressure was 100/70 mm.Hg. There was no shock during the operation. However, in the immediate postoperative period there was an abrupt drop in blood pressure to 70/40 mm.Hg. accompanied by respiratory difficulty and marked shift of the mediastinum to the right. The respiratory distress and mediastinal shift were corrected by the aspiration of bloody fluid and air from the left chest, after which the blood pressure recovered to a level of 85/55 mm.Hg. and reached normal two days later. Fifteen hundred cubic centimeters of 5 per cent glucose in water plus sodium sulfadiazine were given the afternoon of the day of operation. Mental dulness bordering upon stupor was present through the afternoon and night. The next morning the patient was found to be anuric. Spectrophotometric examination of the blood plasma disclosed the presence of a severe hemolytic transfusion reaction. A roentgenogram disclosed left pleural effusion and atelectasis. The blood N.P.N. was 70 mg. per cent, the serum chlorides 86 mEq./L and the serum CO_2 27.8 mEq./L. She was given 80 cc. of molar sodium lactate in 2,000 cc. of 5 per cent dextrose in water intravenously and 500 cc. of Type-O blood. In the 24 hours of the first postoperative day, 80 cc. of black urine were obtained from an inlying catheter. Tables V, VI, VII and VIII list the pertinent chemical findings and fluid balance data from this day onward. The fluid taken by mouth throughout the postoperative period was negligible in amount.

On the second postoperative day the patient was alert and comfortable. Laboratory data showed: blood N.P.N. 86 mg. per cent, B.U.N. 81 mg. per cent, serum chlorides 92 mEq./L, serum CO_2 29.2 mEq./L, serum sodium 133 mEq./L, serum potassium 5.2 mEq./L, and plasma protein 5.1 Gm. per cent. In the 24 hours of the second postoperative day she was given 2,000 cc. of 10 per cent glucose in water and 1,000 cc. of whole blood. Her urine output in this period was 50 cc.

On the afternoon of the second postoperative day peritoneal irrigation was instituted. An inflow tube and a sump-drain were introduced into the lateral aspects of the peritoneal cavity under local anesthesia and peritoneal irrigation at a rate of 40 cc./min. was started. The inflow fluid was passed through a Mandler (Berkefeld) filter. Penicillin and Vitamins B, C, and K were given parenterally each day. Irrigation proceeded smoothly, produced no discomfort and required no adjustment to maintain outflow. Because of recurring respiratory difficulty the patient remained in a high sitting position, which is not optimal for peritoneal irrigation.

On the third postoperative day the patient seemed well except that respiratory distress required two taps of the left chest which yielded about 2,000 cc. of bloody fluid. The blood N.P.N. was 70 mg. per cent and serum CO_2 23.3 mEq./L. She was given 2,600 cc. of 5 per cent glucose in water and 500 cc. of blood. The urine output was 30 cc. A menstrual period began. In view of the uterine bleeding and the reaccumulation of bloody fluid in the left chest, the danger from heparin in the irrigating fluid was considered but since the blood clotting time and prothrombin time were found to be normal repeatedly, heparin in the irrigating fluid was continued. The outflow fluid had a slightly uriniferous color and odor. The blood pressure had risen to 180/90. The extracellular fluid space, as measured by radioactive sodium, was found that evening to be 15,000 cc. or 29.5 per cent of the body weight (50.9 Kg.), a considerable increase over the normal extracellular space, which is 18–22 per cent of

body weight. This suggested the development of edema, which was not yet obvious clinically. It is possible that the chest fluid and the intraperitoneal fluid may have accounted in part for the increased extracellular fluid space.

The presence of edema was evident the next (fourth) day. Another chest tap was required and removed a liter of brown fluid. A transfusion of 500 cc. of blood and 2,000 cc. of 15 per cent glucose in water were given intravenously. The urine output for the day was 60 cc. The plasma sulfadiazine level was 4.9 mg. per cent, derived entirely from the irrigation fluid. Thereafter it was omitted from the irrigation fluid because of the remote possibility that it might retard renal recovery. Chest signs indicative of slight pulmonary edema were found. Digitalization was begun.

On the fifth postoperative day the patient's respirations were rapid, deep and labored. There was no evidence of recurrence of pleural effusion and the respiratory changes were attributed to a combination of pulmonary edema and acidosis. The serum CO_2 was 16.9 mEq./L, serum chlorides 110 mEq./L, blood N.P.N. 70 mg. per cent, B.U.N. 45 mg. per cent, plasma protein 5.0 Gm. per cent and the venous blood pH 7.38. By the dye and hematocrit methods the blood volume was found to be 3,500 cc. (7.1 per cent of body weight) and the plasma volume 1,950 cc. (4.0 per cent of body weight) — both values being somewhat lower than normal. Generalized edema was marked. The extracellular "thiocyanate space" was 29,400 cc., or 58 per cent of body weight. Part of this increase may have been due to an intracellular shift of normally extracellular ions as indicated by the somewhat reduced serum sodium (131.0 mEq./L.) and elevated serum potassium (6.2 mEq./L.). Fifteen hundred cubic centimeters of 10 per cent glucose in water and 600 cc. of plasma were given through the day.

By midnight the dyspnea was very marked and was not relieved by the aspiration from the left chest of 300 cc. of fluid. To reduce pulmonary edema 800 cc. of a solution containing 30 per cent glucose and 25 per cent human albumin was administered intravenously in a period of 5.5 hours. At the end of this time severe pulmonary edema with extreme dyspnea, frothy sputum, cyanosis, and loss of consciousness was manifest. Treatment included morphine (8 mg.), atropine (0.65 mg.), continuous oxygen inhalation at a positive pressure of 1 cm. of water, phlebotomy of 300 cc. and the application of venous tourniquets to the extremities. Gradual improvement occurred over a period of three hours, leaving the patient conscious but dyspneic, with poor color and with râles throughout both lungs. In the hope of removing the excess water from the patient's body by way of the peritoneal membrane, almost all sodium (as well as all other electrolytes) were eliminated from the irrigation fluid, which was made hypertonic by a combination of 5 percent gelatin and 2.5 per cent glucose. The Mandler filter was removed from the inflow circuit to allow the free passage of the gelatin. Irrigation with this solution was begun at noon of this day. By early evening the pulmonary edema seemed considerably diminished. At 10:30 P.M. the patient was found to be in extreme shock, unconsciousness, with cold, pale skin and a thin weak pulse. The systolic blood pressure which had been at a level of 150 mm.Hg. all through the day up to 6:00 P.M. was now unobtainable. The irrigation was stopped and 100 cc. of 50 per cent glucose plus 500 cc. of blood were given intravenously. The systolic blood pressure was restored to 110 mm.Hg. by midnight and it remained at that level. A slow intravenous drip of 30 per cent glucose in water was continued. Respirations remained labored and the patient remained unconscious.

The next morning the patient was still unconscious. The coma was attributed to cerebral edema. The generalized and pulmonary edema seemed definitely diminished. The blood N.P.N. was 42 mg. per cent, the B.U.N. 40 mg. per cent and the serum CO_2 20.4 mEq./L. To further reduce the edema, particularly the cerebral edema, peritoneal irrigation with 5 per cent gelatin, and 2.5 per cent glucose was resumed at noon. Within 30 minutes the blood pressure dropped to 80/50 mm.Hg. and in the subsequent 2.5 hours to 60/40, after which the irrigation was stopped and the systolic pressure

slowly returned to 100 mm.Hg. A generalized tonic and clonic convulsion, accompanied by apnea, lasting one minute, occurred. There was a marked rise in hemoglobin concentration and hematocrit from the previous day's levels of 11.6 Gm. per cent and 42 per cent, respectively, to 15.8 Gm. per cent and 57 per cent, respectively, and a concomitant fall in serum sodium and chloride from 131 and 106 mEq./L., respectively, to 114 and 88 mEq./L., respectively. Eighty cubic centimeters of molar sodium lactate was given intravenously because of the low serum sodium. The peritoneal irrigating fluid was changed to a simple solution of 5 per cent glucose in water which was brought to the physiologic concentration of sodium and chloride by the addition of sodium lactate and sodium chloride.

At 2:30 A.M. of the eighth postoperative day, the seventh day of peritoneal irrigation, convulsions recurred, the blood pressure dropped and in spite of treatment in the next four hours with sodium phenobarbital, sodium lactate and whole blood transfusion, the patient died. By the time of death the subcutaneous edema had disappeared.

The patient had never shown systemic or any local evidence of sepsis during her illness. The rectal temperature remained below 100° F. in the early postoperative days and she was completely afebrile in the two days before death. Histologic examination of the output fluid showed no leukocytes. On the last day of irrigation a very few colonies of bacteria were grown from the outflow fluid. These were identified as *Staph. albus, E. coli, Cl. welchii* and diplococci of the enterococcus type.

Postmortem examination showed typical transfusion reaction kidneys, but no other cause of death. There was no peritonitis, adhesions or evidence of tissue injury in the peritoneal cavity. Subcutaneous and cerebral edema were absent and pulmonary edema was minimal.

The report of the completed examination of the kidneys is not yet available.

COMMENT: This patient was given 500 cc. of incompatible blood while under general anesthesia and became almost completely anuric immediately thereafter. She excreted no more than 80 cc. of urine on any of the subsequent eight days of life. Peritoneal irrigation for approximately six of those days was successful in reducing the blood N.P.N. level to near normal limits. The irrigation proceeded with a minimum of adjustment, produced no discomfort, caused no intra-abdominal damage or infection, and did not interfere with the remainder of the care of the patient.

Death probably was due to incorrect management of the water balance problem. This may have been due in part to a division of responsibility in the management of this patient between ourselves and the resident staff at the hospital at which the patient was being treated. She received water in excess, as the fluid intake data demonstrated. At least partly because of this (there is also a possibility that water might be absorbed in excess of normal requirements from the irrigating fluid) she developed pulmonary and probably cerebral edema. The water was given as a vehicle for glucose to counteract starvation and acidosis, but the glucose could have been given in much higher concentration and smaller fluid volume. When the tissue edema was massive and pulmonary edema severe, hypertonic glucose was given, but concentrated albumin was also given and both were given too rapidly. Even though the plasma volume was a little less than normal, the addition of concentrated albumin proved to be unwise since the resulting rapidly induced hydremic plethora precipitated an even more severe pulmonary edema with

the disastrous results described. The treatment then needed to correct the situation resulted in a considerable depletion of an originally less than normal blood volume. The administration of oxygen at positive pressure in expiration as well as in inspiration may have further reduced cardiac output. The subsequent use of an hypertonic and salt poor irrigation fluid to reduce the edema may have reduced plasma volume more rapidly than it could be restored from interstitial fluid, so that while pulmonary edema diminished, extreme shock developed and was unrecognized for several hours, during which the patient was in a high sitting position with a very low blood pressure. Shock was subsequently corrected, but the period of poor blood flow may well have done damage which contributed to the fatal outcome. The patient never regained consciousness thereafter. A second period of peritoneal irrigation with hypertonic salt-poor fluid resulted in another drop in blood pressure.* A marked rise in hematocrit and hemoglobin concentration substantiated the impression that the plasma volume was being too rapidly reduced.

The terminal convulsions are not explained except on the basis of cerebral damage from the antecedent edema or shock or possibly because of reduced ionizable calcium, because calcium was omitted from the irrigating fluid in the last two days and the plasma calcium concentration did drop somewhat below normal.

There is no way of knowing if or when recovery of kidney function might have occurred. The dose of incompatible blood was large, but there is no reason to believe that renal healing might not have taken place if the patient could have been kept alive for the required time.

The electrolyte pattern of the plasma was kept near normal limits. Figure 7 is the diagram adapted from Gamble,[6] showing the electrolyte composition of the plasma of the patient on the sixth day of almost complete anuria (day 5, Table V) compared with that of normal plasma. On this day the patient's serum CO_2 concentration was the lowest recorded, but normal blood pH was maintained nevertheless.

The total disappearance of the edema before death was ample testimony to the efficacy of peritoneal irrigation with hypertonic solutions, for removing water from the body. In spite of the complex and disappointing developments peritoneal irrigation served its primary purpose. But it is at the same time evident that such a tool for the control of fluid and electrolyte balance cannot be successfully instituted without the exercise of extreme caution and without well considered judgment as to the kind of supplementary therapy needed for nutritional balance.

Discussion.—The foregoing experiences show emphatically that this method is still in the experimental stage. What is so far established is

* This happened so quickly that a toxic effect of the solution was suspected. To exclude the suspicion of toxic material in the irrigation solution, 300 cc. of the solution was given intravenously during 2–3 hours to an 8-Kg. dog without immediate or delayed harmful effect.

TABLE V

CASE 4: DAILY BLOOD ANALYSIS

Day*	Blood N.P.N. Mg. %	Blood Urea N Mg. %	Serum CO^2 mEq./L.	Serum Chloride mEq./L.	Serum Sodium mEq./L.	Serum Potassium mEq./L.	Serum Calcium Mg. %	Serum Phosphorus Mg. %	Serum Protein Gm. %	Serum Magnesium mEq./L.	Venous Blood pH
1	7)		27.8	86					5.1		
2	86	81	29.2	92	133	5.7					
3	70	69	23.3	94					5.1		
4	90	51	21.7	102	132	6 2			5.0		
5	70	45	16.9	110			7.8	5.8	5.0		7.38
6	60	42	22.2	106	131	5.5	7.8	6.8	5.7	2.4	
7	42	40	20.4	88	114	7.1	8.0	6.7			

* Days subsequent to transfusion reaction.

(1) that a properly performed peritoneal irrigation can eliminate all clinical and chemical evidence of the uremic state; (2) that significant improvement can be achieved within 36 to 48 hours; (3) that the total time required will vary with the duration and severity of the uremia, degree of saturation of the tissues with retained products, degree of dehydration or edema, the nutritional state, food intake, the rate of protein catabolism, the presence of associated disease and the rate of efficiency of peritoneal irrigation; (4) that irrigation will not injure the peritoneal structures; and (5) that the efficiency

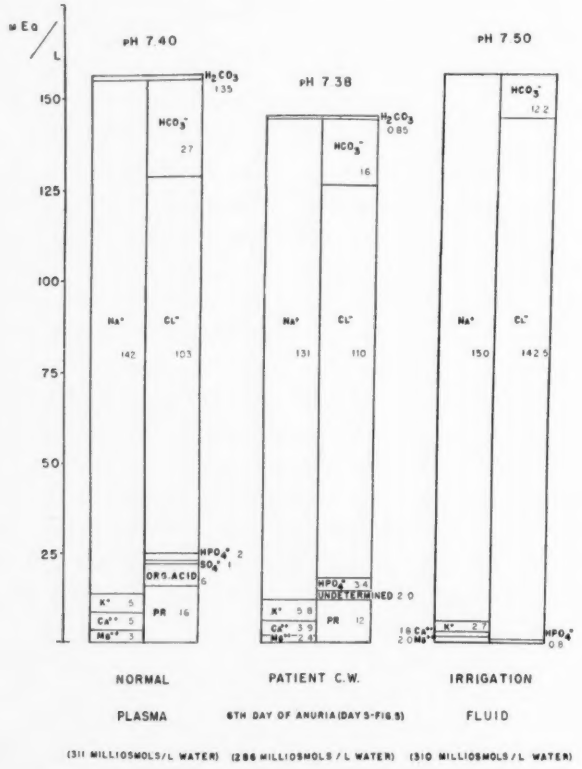


FIG. 7.—Gamble diagram[6] of the electrolyte composition of normal plasma, the plasma of Case 4, and of the peritoneal irrigation solution.

of irrigation so far as blood urea clearance is concerned does not diminish with time and exceeds the minimal degree (10 per cent–15 per cent) of renal excretory function necessary to avoid reaccumulation of nonprotein nitrogen or urea.

It is possible that the uremic state imposes a further burden on the damaged kidneys, as it does on all other tissues and that the repair of the renal injury is facilitated by the removal of the uremic state. The time necessary for repair of the renal injury and recovery of sufficient renal function can not be foretold. It will vary from one type of injury to another and from case to case with the same type of injury. Lesions capable of repair within a few weeks should be amenable to this therapy because it probably can be continued safely that long. To date the longest period we have carried the treatment is 12 days.

The danger of peritonitis has been the chief hazard. With the introduction of a bacterial filter on the inlet side of the irrigating system, with chemotherapy and with careful isolation of the abdominal wounds and tubes by proper dressings, this danger is minimized very substantially. The organisms isolated from the peritoneal drainage fluid were *E. coli* after 12 days in Case 2, *E. coli* after three days in Case 3, in which it produced no significant clinical effects, and *E. coli, Cl. welchii, Staph. albus* and enterococci in Case 4, in which at postmortem there was no evidence of peritonitis. Objection to sulfonamides on the ground of inflicting additional renal injury may be valid and may justify restricting chemotherapy to penicillin and streptomycin when available. The placing of the inflow and outflow tubes should be done with such care that the possibility of dislodgement and the need to replace them should be avoided. It is certain that a rubber catheter of whatever design as an outflow tube will not answer this need and should not be attempted. A sump-drain made of inert metal (stainless steel) is completely satisfactory and devoid of discomfort to the patient.

The most meticulous attention to fluid and electrolyte balance is continuously required. Neglect to do so, as Case 4 demonstrates, will vitiate the whole effort. In uremia "the defense of the chemical structure of the extracellular fluid is of much more importance from the point of view of survival than reduction of azotemia."[7]

Pulmonary edema was present in Cases 2, 3 and 4 — in all instances because of the intravenous administration of fluid in excess of tissue requirements for fluid in the anuric state and because of acidosis. The fluid requirement during renal suppression consists only in water lost by vaporization, which is about a liter per day, *i.e.*, 0.5 cc./Kg./hr.,[6, 8] unless fever, vomiting, diarrhea or sweating are present. All these patients received water in excess of what they required; Cases 2 and 3 before irrigation was started, in what was an obviously futile effort to stimulate diuresis; Case 3 for the first two days after it was started, and Case 4 for five days after irrigation was started. Since food intake is likely to be either inadequate or *nil*, intravenous fluid is necessary purely as a vehicle for glucose (and possibly for

amino-acids if treatment is needed for many days) to counteract starvation acidosis and to spare protein breakdown, but the fluid must be given in as small a volume as possible. Four hundred grams of glucose in 1,200 cc. of water should substantially satisfy the caloric need and prevent acidosis. It should be given slowly to avoid hydremic plethora and rapid loss of glucose into the irrigating fluid.

TABLE VI

CASE 4: DAILY URINE OUTPUT AND INTRAVENOUS FLUID ADMINISTRATION

		Fluid Intake					
Day	Urine Output Cc.	Blood Cc.	Plasma Cc.	25% Albumin Cc.	Water Cc.	Dextrose in Water %	Fluid Removed from Left Chest Cc.
0	0	500			1500	5	± 300
1	80	500			2000	5	
2	50	1000			2000	10	
3	30	500			2600	5	2000
4	60	500			2000	15	1000
5	±60		600		1500	10	
6	±60			50	800	30	300*
7	±60						

* 300 cc. venesection.

TABLE VII

CASE 4: URINE ANALYSIS

Day	N.P.N. Mg. %	Urea N Mg. %	NH^3 N Mg. %	Creatine Mg. %	Creatinine Mg. %	Gross and Microscopic Appearance
2	410	128				Black, turbid, loaded with débris; no casts or R.B.C.
3		70	55			
4	410	95		0	24	Dark brown, clear
5		40	0			
6	92	29		0	24	Amber, clear, acid, albumin 4+; many R.B.C.

TABLE VIII

CASE 4: UREA REMOVAL BY PERITONEAL IRRIGATION

	Peritoneal Fluid				
Day	Volume Cc.	Flow Rate Cc./Min.	Urea N Mg. %	Total Urea Gm.	Blood Urea Clearance by Peritoneum Cc./Min.
2	38,000	26.5	23.3	17.7	7.6
3	38,000	26.5	20.6	15.7	7.9
2	34,000	23.6	21.0	14.3	9.7
5	18,000	16.6	34.0	12.3	12.5

It is difficult to predict the exact state of affairs with reference to excretion and absorption across the peritoneal membrane with the type of irrigating fluid used and a varying state of hydration of the plasma and extracellular fluids. It is not known whether, with the type of fluid used, irrigation offers a route of exit for excess body water. We suspect that

the fluid as at present constituted is not satisfactory for this purpose. Experience with Case 4 indicates that when the peritoneal fluid is made hypertonic by 5 per cent gelatin and 2.5 per cent glucose, water can be so rapidly removed from the plasma that caution should be exercised to avoid excessive hemoconcentration. Eventually it may prove desirable to modify the electrolyte composition of the irrigating fluid, for better control of acidosis by reducing the chloride content to that of normal plasma and substituting sodium lactate buffered with lactic acid. Further, an increase in the glucose of the irrigation fluid might provide a sufficient amount to balance what is lost into the peritoneal fluid from the intravenously administered glucose, to counteract water absorption from the irrigating fluid and to provide some of the glucose for metabolic needs. If modifications needed for such purposes result in making the fluid hypertonic, their long-continued use might be impractical, because of the potentially irritating properties of such solutions. Further data will be accumulated to discover the optimal solution under most circumstances.*

The proper time to institute peritoneal irrigation is not established. It is not possible to say when any given data regarding the uremic state signify the existence of irreversible damage. Therefore, since the method can be carried on for many days safely it should be started soon after the uremia is full-blown. Meanwhile it is important not to add to the patient's burden by the harmful effects of excessive water administration, since the amount of water needed is small and as a diuretic it is futile. The time for discontinuing peritoneal irrigation can be determined readily by measurements of the return of sufficient kidney function to prevent azotemia and to sustain a normal fluid and electrolyte balance.

CONCLUSIONS

1. Continuous peritoneal irrigation with an appropriate fluid is a satisfactory method of eliminating uremia. It can be used in any case of acute renal failure in which death from uremia is likely and in which recovery of kidney function is considered possible.

2. The control of fluid and electrolyte balance is at least as important as the elimination of nitrogenous waste products, and is an integral part of this therapeutic method.

---

* Since submitting this article for publication additional clinical experience (to be published) has demonstrated that the use of 2% glucose in the irrigating fluid instead of glucose at blood level concentration will prevent the production of edema from the absorption of water from the irrigating fluid. Furthermore, the absorption of glucose from 35 liters of such irrigating fluid in 24 hours was found to be some 200–300 grams of glucose. The absorbed glucose therefore reduces the basal requirement of a starving patient from 400 to 100–200 grams per 24 hours, and so reduces the amount that must be administered intravenously to prevent starvation acidosis. Two per cent glucose, moreover, is not irritating to the peritoneum.

BIBLIOGRAPHY

1 Seligman, A. M., Frank, H. A., and Fine, J.: Treatment of Experimental Uremia by Means of Peritoneal Irrigation. J. Clin. Invest., **25**, 211, 1946.

2 Frank, H. A., Seligman, A. M., and Fine, J.: The Successful Treatment of Uremia following Acute Renal Failure by Peritoneal Irrigation. J. A. M. A., **130**, 703, 1946.

3 Putnam, T. J.: The Living Peritoneum as a Dialyzing Membrane. Am. J. Physiol., **3**, 548, 1923.

4 Van Slyke, D. D., Stillman, E., Moeller, E., Ehrlich, W., McIntosh, J. F., Leiter, L., MacKay, E. M., Hannon, R. R., Moore, N. S., and Johnston, Ch.: Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy. Medicine, **9**, 257, 1930.

5 Ryder, H. W., Sharer, M., and Ferrin, E. B.: Salicylism Accompanied by Respiratory Alkalosis and Toxic Encephalopathy. N. E. Jour. Med., **232**, 617, 1945.

6 Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. Lecture Syllabus, Harvard Medical School, 1942.

7 Gamble, J. L.: Personal communication.

8 Butler, A. M., and Talbot, N. B.: Parenteral Fluid Therapy. N. E. Jour. Med., **231**, 585 and 621, 1944.

DISCUSSION.—DR. ARTHUR B. MCGRAW, Grosse Pointe, Mich.: I wish to add a very incomplete report on one patient, upon whom an attempt was made to use this method of Doctor Fine's. Five days before this meeting, our Pediatric Department asked me to help them set up an irrigation system such as Doctor Fine describes. We had no sump-tube of the size described by him, but we did have one small abdominal suction tube of brass, chrome plated and rather worn. We cut it down to what we felt was the proper size.

The patient was an anemic anuric six-year-old boy, suffering from glomerulonephritis superimposed on a severe nephrosis. It worked very well for one day and night, and the next day. On the third day we had a little trouble with the outflow of the tube and I think that in trying to wipe that out we may have introduced contamination into the peritoneal cavity. On the fourth day it stopped, and when I left we had decided to take it out, leave it out overnight, and then reinsert it in another location. I can only report that the child's nonprotein nitrogen dropped progressively in four days from 150 to 95. I think this is an interesting method, and it holds great promise. If we try it again with more precautions and more careful teamwork, I believe we can achieve successes such as Doctor Fine reports.

DR. EDWARD D. CHURCHILL, Boston, Mass.: The type of case selected by Doctor Fine for experimental observations tends to obscure the broad surgical application of such a method when it is perfected and ready for general clinical application. It may not be realized that, despite all the optimistic reports on the successful management of shock in this war, renal shutdown was the stone wall against which we butted our heads many times. The reduced blood volume of shock could be corrected by transfusion, but the kidneys ceased to function and many wounded men died despite the most skilled surgical procedures. The full explanation is still not clarified; the problem requires further study. The surgeons caring for these patients with anuria tried many forms of treatment: high spinal anesthesia; alkalies, to the point of severe alkalosis; and many other measures. Still the patients died in uremia. Doctor Fine's method represents one more procedure that may be applicable to men suffering from renal shutdown following severe trauma. I hope it will prove successful.

DR. ALLEN O. WHIPPLE, New York City: I have been tremendously interested in this new experimental work. Doctor Fine told me about it a few days ago, and I think he has established a point of departure in the treatment of anuria and uremia which will apply not only to surgical but to medical cases, and is a real advance. One

point he has emphasized is the difficulty of maintaining an adequate system of intake and output in the peritoneum. The peritoneum, fortunately, has the greatest capacity for obstructing anything you put into it and shutting it off, of any tissue in the body. We have been interested in this problem in patients with ascites, in an attempt to shunt the fluid into the ureter, and our problem has been that of preventing the peritoneum from shutting off any anastomosis we made. We have not succeeded as yet in devising any method to avoid blocking and plugging of any apparatus we have introduced into the ureter.

DR. ALTON OCHSNER, New Orleans, La.: Some of the original work on this problem was done by Sidney Bliss. About 15 years ago he showed that a bilateral nephrectomy could be kept alive with normal urea content of blood for many weeks. He showed also that much less effectively this could be accomplished by gastric lavage. We have had two patients who had almost complete renal shutdown due to incompatible blood. One was a young woman in whom the reaction was not recognized for 26 hours after transfusion. The nonprotein nitrogen started to go up—to 190. She was started on gastric lavage, using as much as 20 liters of fluid in the 24 hours, and it was brought down to less than 70 and maintained at that level until the urinary function returned.

The other patient, a man, also had an incompatible blood reaction; he had a bad kidney function to begin with. He was treated with gastric lavage with large amounts of fluid. The first case required about two weeks and the second ten days. We have been afraid of peritoneal lavage, and I believe the same results can be obtained by gastric lavage if large amounts of fluid are used.

DR. JONATHAN E. RHOADS, Philadelphia, Pa.: We approached this problem in a much less thorough manner in 1938, in two patients, introducing fluid, a liter at a time, through a cannula into the peritoneal cavity. Large amounts of urea were recovered in the solution when it was allowed to drain out. In reviewing the literature it was found that substitution methods of treating renal failure go back to 1913, when Abel, Rowntree and Turner set up a system of celloidin tubes through which the blood of animals was circulated. A further study was made in Germany by Haas, and Gantner suggested the use of the peritoneal lining as a dialyzing membrane. His experiments were successful chemically, but, in general, the patients in which the method was used were not capable of recovery.

It is now easier to employ the method of Abel, Rowntree and Turner, because suitable tubes for dialysis can be obtained in the form of sausage casing, which is available in lengths of 100 feet. About two years ago Dr. Henry Saltonstall and I set up a system using 60 feet of this tubing in a bath of Ringer's solution with sufficient gelatin to counteract the osmotic pressure of the serum proteins, and by heparinizing the patient it was possible to allow his blood to flow out from an artery through this system and to reënter the circulation through the veins. This method, too, will reduce the urea nitrogen.

DR. RALPH COLP, New York City: The method which Doctor Rhoads has described was the subject of a thesis by Doctor Kolff of Amsterdam, Holland, published in January, 1946. I have an abstract of it prepared by Dr. I. Snapper, and I think that some of the pictures might clarify some of the statements Doctor Rhoads has made. (slide)

"Doctor Kolff emphasizes that the construction of an efficient artificial kidney has only been possible since an efficient anticoagulant, heparin, and a good dialyzer consisting of a cellophane tube, 23-mm. wide and 50 yards long, have become available. The cellophane tube is wound spirally around a cylinder which consists of a wooden lattice with a coat of lacquer (Fig. 1). This cylinder rotates slowly and the lowest part of the cylinder is submerged in a tank (Fig. 2) containing 70–100 liters of a

solution of 0.6% NaCl, 0.2% $NaHCO_3$, 0.04% KCL and 1.5 to 2% glucose. A glass cannula is tied into a vein on the dorsum of the foot, or in the forearm, and a slow infusion of salt solution is started. Then another glass cannula is tied into the radial artery. After this, the patient is heparinized with 1,200 milligrams of heparin or more. The glass cannula in the artery is connected by a rubber tube with the cellophane tube. As the cylinder is turned continuously after it has migrated through the entire length of the cellophane tube, it is transported *via* another rubber tube to which a small pump has been attached to the cannula which has been tied in the vein.

"The cellophane tube is only partially filled with blood, so that the blood is spread over a large surface which greatly increases the rate of dialysis. During the passage of the blood through the cellophane tube, large amounts of crystalloid substances of the blood are removed by dialysis. Since no calcium can be present because of the $NaHCO_3$ content in the fluid against which the blood is dialyzed, calcium is also removed from the blood. It is, therefore, necessary to give one or two intravenous injections of calcium gluconate to the patient slurring the dialysis.

"The dialysis lasts 10–14 hours. After the dialysis is finished, the cannulas in artery and vein are closed off and left *in situ* for 24 hours. When the coagulation time of the blood has returned to normal, the cannulas may be removed. The salutary effect of the vividialysis in the artificial kidney is demonstrated by the amount of urea which is removed from the blood during this period. The largest quantity of urea dialyzed out amounted to 260 Gm. Even in cases in which the blood urea nitrogen before dialysis had risen to 160 mg. per cent, one dialysis was sufficient to reduce this value to 45 mg. per cent. At the same time the increased nonprotein nitrogen, uric acid, creatinin and indoxyl of the blood fell to nearly normal values, and the xanthroprotein reaction of the serum diminished significantly. Clinical signs of uremia usually disappeared within 24 hours. It is evident that the artificial kidney will only have a temporary effect in patients with chronic nephritis and uremia. However, in instances in which an individual with previously competent kidneys suddenly develops loss of renal function, the artificial kidney may well have a life-saving action. Kolff cites two cases in which survival of the patient has at least been due to the purification of the blood in the artificial kidney."

Dr. Jacob Fine, Boston, Mass. (closing): I am very grateful for this discussion. Some of the points brought up are dealt with in the body of the paper. I should like to underline Doctor Churchill's warning that this is still a highly experimental phase of the problem and is not presented as a satisfactory clinical method as yet. The method of external dialysis might prove satisfactory. Our objection to it is that it imposes an arteriovenous anastomosis on an already seriously ill patient. Continuous irrigation of the gastroduodenal tract will remove some excretory products. It is our view that not enough will be removed by this route to cure azotemia or restore electrolyte balance in persistent and total renal suppression.

Doctor Whipple referred to the difficulty with plugging of the tubes. We have fully obviated this with the stainless steel sump-drain for drainage. The inlet catheter, so far in our experience, has not plugged so long as fluid is kept running in. Irrigation proceeded smoothly with the sump-drain in the last two patients, in one for seven and in the other for six days without discomfort. The tube should be directed down into the cul-de-sac. The drainage fluid must be watched to see when bacteria first appear, so as to introduce appropriate chemotherapy if needed.

I have nothing to add in reference to Doctor McGraw's experience with the child with nephrosis. If there is some likelihood that the renal lesion is reversible in a few weeks' time, we believe this method will be advantageous, but we are not prepared to say whether any form of nephritis or nephrosis is suitable. In renal injury from incompatible blood, the method keeps the patient free of uremia during the period of shutdown and may shorten the time of healing and recovery of renal function.

THE SURGICAL TREATMENT OF CONGENITAL PULMONIC STENOSIS*

ALFRED BLALOCK, M.D.

BALTIMORE, MD.

FROM THE DEPARTMENT OF SURGERY OF THE JOHNS HOPKINS UNIVERSITY AND THE JOHNS HOPKINS HOSPITAL, BALTIMORE, MD.

PRIOR TO THE INITIATION[1] of the work to be discussed in this paper only one attempt had been made by operative means to treat patients with pulmonic stenosis. This attempt was made by Doyen[2] in 1911, the procedure consisting of division of the constricted area with a tenotome knife. The patient died shortly after operation. In patients with congenital pulmonic stenosis the constricted or atretic area is usually not in the valve but is in the pulmonary conus itself. It is doubtful if incision or partial excision of the stenotic area would result in permanent improvement; it appears likely that the area would subsequently become stenosed again. These considerations led to an attempt to treat the condition by a different type of operation.

Many experiments[3, 4] preceded the first attempt to increase the pulmonary blood flow of patients. It was demonstrated first that one can anastomose without great risk the end of one of the arteries arising from the arch of the aorta to the side or to the distal end of one of the two pulmonary arteries of anesthetized dogs. In subsequent experiments, after a high degree of chronic arterial unsaturation had been produced, it was found that the creation of an artificial ductus arteriosus resulted in an elevation in the oxygen saturation of arterial blood.

When the problem was transferred from the experimental animal to the patient, it was thought that a moderate degree of improvement would result in the patient with pulmonic stenosis if the pulmonary blood flow were increased. The improvement in most cases has been much more striking than had been anticipated. Some of the results will be described later in this paper.

The main indication for operation is evidence of an inadequate flow of blood to the lungs. Important in the diagnosis is the absence of visible pulsations in the lung fields as observed under the fluoroscope and roentgenographic evidence that the pulmonary artery is small in size. The typical case of the "tetralogy of Fallot" should not present great difficulties in diagnosis. There are, however, many borderline cases in which it is difficult or impossible to be certain of the true nature of the condition. If under such circumstances the patient has a hopeless prognosis without an operation, Dr. Taussig and I have taken the position that an exploration is indicated. If doubt still exists after the pulmonary artery is exposed, the pressure in the artery is measured by using a needle and a water manometer. When the pressure is greater than 300 mm. of water, it is our opinion at present that an anastomosis is probably inadvisable.

* Read before the American Surgical Association, April 2–4, 1946, Hot Springs, Virginia.

The limits as to age-groups suitable for the operation have not been established. The operation has been performed successfully on an infant of five months and on an adult of 21 years. The operation was attempted on an infant two months of age, but there was atresia of the pulmonary orifice and the artery was diminutive in size, and an anastomosis could not be performed. It is believed that the age-period of two years to ten years is the most desirable one in which to perform the operation.

Although most of the children have had visible cyanosis when at rest, one should not be misled by the absence of cyanosis if the patient has little or no tolerance to exercise. Under such circumstances the arterial oxygen saturation should be determined under basal conditions and immediately following exercise. If there is definite decrease in the saturation with exercise and if inadequate pulmonary blood flow is believed to be the cause, an operation should be seriously considered. Several of our most gratifying results have been in patients of this type.

There have been a few alterations in operative technic during the past year. Probably the greatest has been in connection with the side of the chest on which the operation is performed. It was held originally that the approach should be made on the left if one wishes to utilize a subclavian artery for the anastomosis. This view has been altered, and it is believed now that one should make the approach on the side on which the innominate is located. This is usually, but not always, the right side. If the aorta descends on the right, the innominate artery is located on the left rather than the right. Such has been the position in more than 20 of our patients. Fortunately the position of the aorta can be determined preoperatively by employing the method of Bedford and Parkinson.[5] If one makes the approach on the side on which the innominate artery is located, one may choose the innominate artery, the subclavian artery, or the carotid artery for the anastomosis depending upon the existing inadequacy of the flow of blood to the lungs and the sizes of the available vessels. The choice of vessels is not always an entirely free one because in some instances the innominate or the subclavian artery may be too short for the desired purpose and the longer vessel must be chosen. Exposure of the innominate artery not only offers a wider choice of vessels but is of advantage in case the subclavian artery is used. After an anastomosis in which the subclavian branch of the innominate is used, the subclavian artery makes an angle of approximately 90 degrees with its parent vessel. The angle is usually a much more acute one when the subclavian branch of the aorta is used. The use of the subclavian branch of the innominate is demonstrated in Figures 1 and 2.

There has been a wide variation in arteries arising from the arch of the aorta. In some instances the four arteries have arisen independently, there being no innominate artery. In several cases the right subclavian artery has arisen on the left and has reached the right arm after passing under the trachea and esophagus. Despite the multiplicity of variations there has been in every case a systemic artery which was suitable for anastomosis to a pulmonary artery.

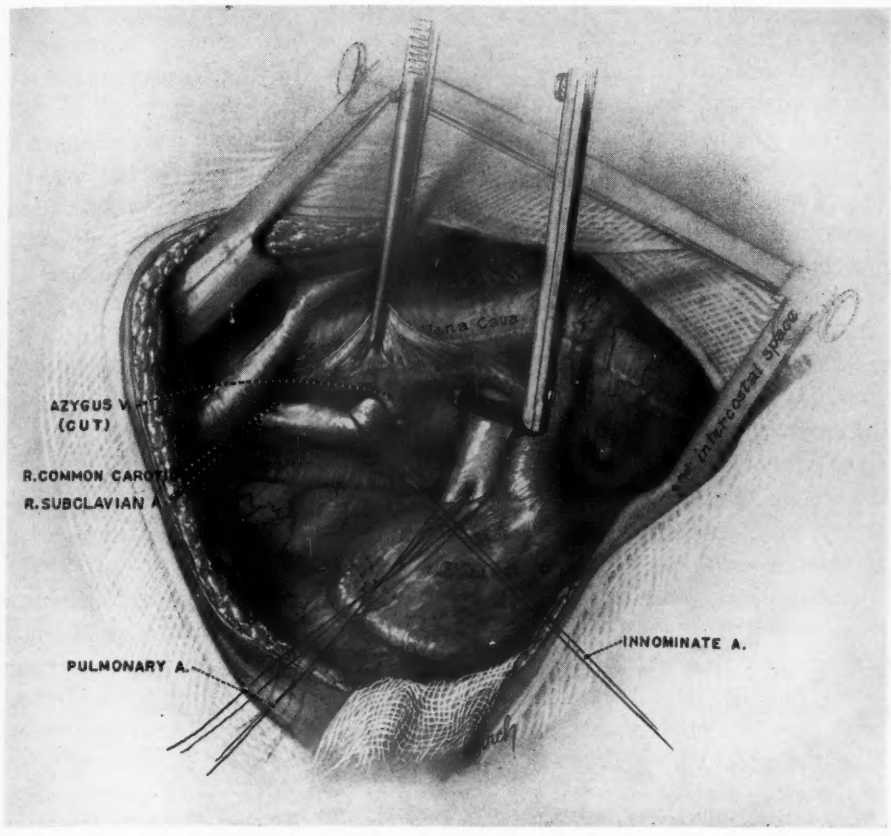


FIG. 1.—Showing the right pulmonary artery, the innominate artery, the right common carotid artery and the right subclavian artery prior to ligation and division.

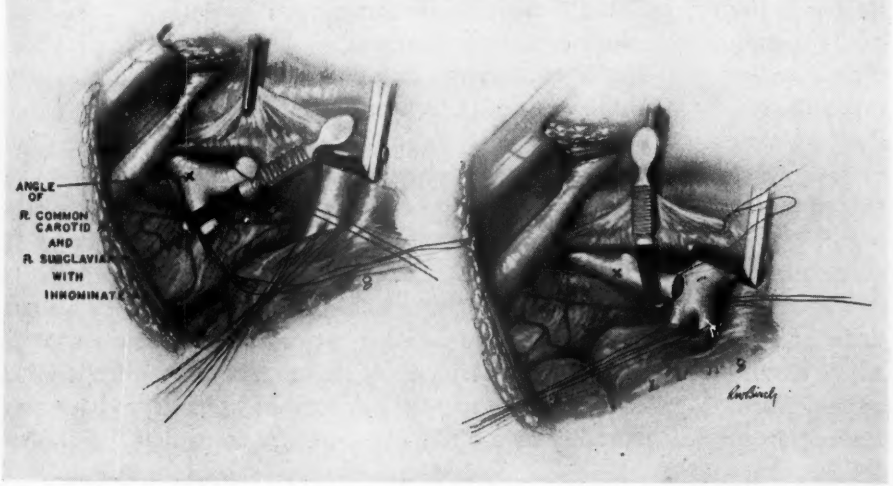


FIG. 2.—Showing the anastomosis of the proximal end of the right subclavian artery with the side of the right pulmonary artery. The transposed subclavian artery makes an angle of approximately 90 degrees with its parent vessel.

Variations in the position and size of the pulmonary artery have been fewer than was anticipated. In one patient the right pulmonary artery could not be found at the time of operation and was located with difficulty at autopsy. It was small and was inferior and posterior to its usual position. In another case the pulmonary artery was lying inferior and posterior to the superior pulmonary vein. Unfortunately, the vein was mistaken for the artery and the anastomosis was performed. Death occurred a short time after operation. In a third patient, an infant of two months with atresia of the pulmonary orifice, the right pulmonary artery was diminutive in size. The lumen of this vessel was only about one-tenth the size of that of the subclavian artery and a satisfactory anastomosis could not be performed. In a number of cases the right main pulmonary artery has been very short because of early branching. In two of the earlier operations the branch to the right upper lobe was mistaken for the main right pulmonary artery. In an occasional case in which the main right pulmonary artery is very short it may be necessary to ligate and divide the vessel and to use the distal end for an anastomosis to the end of the systemic artery. If, however, the pulmonary artery is freed of its pericardial attachments, this procedure will very rarely be necessary.

In evaluating the alterations in the oxygen saturation of arterial blood which result from the operation one should bear in mind that in addition to pulmonary stenosis or atresia, patients with the tetralogy of Fallot have an interventricular septal defect and an aorta which communicates with both ventricles. In other words, the aorta probably always receives some venous blood as well as arterial blood, and one would not expect the arterial blood to reach the normal saturation of 95 per cent, or greater, even when the pulmonary blood flow is definitely increased by the creation of an artificial ductus. In view of the septal defect and the overriding aorta it is rather surprising that the arterial saturation has risen so greatly in many of the patients. Some of the more striking results of the operation are shown in Table I.

The improvement in the general condition of the patients has paralleled the alterations in the saturation of the blood and the decrease in the polycythemia. A change in the color of the mucous membranes is usually apparent shortly after completion of the operation. Cyanosis of the nail beds disappears more slowly and the regression or disappearance of clubbing of fingers and toes requires still longer. A number of the children who could walk only a few feet prior to the operation can now walk a mile or more. Some of the children engage in fairly strenuous exercise.

Operation has been performed upon a total of 110 patients. This figure includes all patients upon whom an incision was made and hence some in whom an anastomosis was not performed. With one exception all operations were performed during the last 14 months. A total of 25 patients have died, making an over-all mortality rate of 23 per cent. A more detailed analysis follows.

In the 110 operations an anastomosis was performed between the end of a systemic vessel and the side of one of the two pulmonary arteries in 91

TABLE I

THE EFFECTS OF AN ARTIFICIAL DUCTUS ARTERIOSUS IN THE TREATMENT OF PULMONIC STENOSIS

Systemic Artery Used	Patient	Age	Art. Saturation Per Cent		Red Blood Cell Count		Hematocrit Reading (Wintrobe)		Result
			Preop.	Postop. (Time After)	Preop.	Postop. (Time After)	Preop.	Postop. (Time After)	
				(111 days)		(111 days)		(111 days)	
Innominate	A. B.	2	28.1	85.3 (55 days)	5,640,000	4,620,000 (55 days)	57.5	38.6 (13 days)	Good
Innominate	J. B.	3	45.9	74.3 (19 days)	7,530,000	5,300,000 (19 days)	68.0	56.0 (19 days)	Good
Innominate	C. C.	4	35.6	77.1 (20 days)	9,630,000	6,170,000 (20 days)	82.0	55.2 (20 days)	Good
Innominate	M. E.	26 Mos.	29.9	71.9 (17 days)	10,010,000	5,950,000 (17 days)	64.3	46.2 (17 days)	Good
Innominate	R. L.	6	22.1	74.8 (2.5 mos.)	11,260,000	6,870,000 (2.5 mos.)	73.2	57.0 (2.5 mos.)	Good
Innominate	M. M.	6	23.4	83.7 (5 mos.)	10,120,000	5,600,000 (5 mos.)	81.0	38.0 (5 mos.)	Good
Innominate	B. R.	12	36.3	86.7 (3.5 mos.)	7,660,000	4,980,000 (3.5 mos.)	71.0	50.0 (3.5 mos.)	Good
Innominate	L. S.	6	38.6	89.9 (20 days)	9,970,000	4,640,000 (20 days)	81.0	46.0 (20 days)	Good
Innominate	B. S.	2	34.0	73.2 (15 days)	9,680,000	7,530,000 (15 days)	72.2	50.2 (15 days)	Good
Carotid	R. L.	3	26.1	81.9 (61 days)	9,080,000	5,200,000 (61 days)	62.4	50.0 (61 days)	Good
Subclavian	S. B.	21	57.7	83.7 (18 days)	7,960,000	6,580,000 (18 days)	81.2	62.5 (18 days)	Good
Subclavian	R. H.	3	32.7	74.0 (4 mos.)	5,660,000	5,340,000 (4 mos.)	58.0	50.5 (4 mos.)	Good
Subclavian	W. L.	3	65.6	84.3 (3 mos.)	6,390,000	4,610,000 (3 mos.)	57.0	41.8 (3 mos.)	Good
Subclavian	S. V. H.	7	49.3	81.1 (35 days)	8,160,000	6,050,000 (35 days)	78.8	56.5 (35 days)	Good
Subclavian	C. W.	3	39.3	75.7	7,480,000	6,690,000	77.0	64.3	Good

patients. There were 16 deaths in this group, a mortality rate of 18 per cent. The subclavian artery was used in 46 patients, with four deaths. One of these was due to hemoptysis on the fifth day which was believed to have been caused by the use of dicumarol. The innominate artery was used in 36 patients and there were 11 deaths in this group. One of these patients was found at autopsy to have a single ventricle with insignificant pulmonary stenosis and another had a transposition of the great vessels which was combined with pulmonary stenosis. The commonest cause of death in this group was cerebral anemia or thrombosis. The end of the carotid was anastomosed to the side of one of the pulmonary arteries in nine patients. There was one death in this group, which occurred nine months after operation. Anastomosis had been performed despite the fact that the patient had a large pulmonary artery with vigorous pulsations. It is believed that this patient had the Eisenmenger complex.

An end-to-end anastomosis was attempted between the end of a systemic artery and the end of one of the two pulmonary arteries in ten patients. This method was used because the pulmonary artery was very short or small or because the patient was extremely ill and haste was necessary. There were four deaths in this series. These four patients had atresia of the pulmonary

orifice and the vessel was too small for a satisfactory anastomosis. In the future an attempt will be made under such conditions to perform the anastomosis between the end of the systemic vessel and a longitudinal opening in the side of the pulmonary artery.

In two patients the right main pulmonary artery was very short and the branch to the upper lobe was mistaken for the main vessel. The subclavian artery was anastomosed to the end of the small artery to the upper lobe. Both of these patients died. In retrospect, it is apparent that the main right pulmonary artery might have been divided and its distal end used for the anastomosis if the condition had been recognized.

Anastomosis was not performed in six patients. In four of these the pulmonary arterial pressure was high and it was thought that anastomosis was not indicated. These patients survived the exploratory operation. The remaining two patients died. In one of these the pulmonary artery was not found at operation and it was located with difficulty at the time of autopsy since it was small and in an abnormal position. In a second patient the chest was simply opened and closed because it was apparent that the patient would not withstand the operation.

In the remaining patient of those who died the right pulmonary artery was inferior and posterior to the superior pulmonary vein. The vein was mistaken for the artery and its side was anastomosed to the end of the carotid artery. The patient died shortly after completion of the operation.

It is of interest that none of the patients had empyema or mediastinitis. Severe bleeding from the anastomosis did not occur postoperatively in any case. There was no significant interference with the circulation of the arm on the side on which the subclavian artery was sacrificed or used for the anastomosis in any of the patients. Weakness or paralysis of the opposite side of the body in patients in whom the innominate or carotid artery was used either had cleared or was diminishing in all who survived the operation.

Although some of the operations were performed too recently to allow an evaluation, it appears that all of the patients with one exception who have survived the performance of an anastomosis are improved. The subclavian artery of this patient was injured by the too vigorous application of the constricting device, and it is probable that thrombosis occurred. It is believed that the artificial ductus in the remaining patients is patent although a murmur cannot be heard in at least one of them. Heart failure or *Streptococcus viridans* endarteritis has not developed thus far in any of the patients.

REFERENCES

[1] Blalock, A., and Taussig, H. B.: The Surgical Treatment of Malformations of the Heart in which there is Pulmonary Stenosis or Pulmonary Atresia. J. A. M. A., **128**, 189, 1945.

[2] Doyen, E.: Chirurgie des malformations congenitales ou acquises du coeur. Cong. franc. de chir., Proc. verb., **26**, 1062, 1913.

[3] Blalock, A.: Effects of an Artificial Ductus Arteriosus on Experimental Cyanosis and Anoxemia. Arch. Surg., **52**, 247, 1946.

4 Blalock, A.: Physiopathology and Surgical Treatment of Congenital Cardiovascular Defects. Bull. New York Academy of Medicine, **22**, 57, 1946.

5 Bedford, D. E., and Parkinson, J.: Right-sided Aortic Arch. Brit. J. Radiol., **9**, 776, 1936.

DISCUSSION.—DR. ALLEN O. WHIPPLE, New York City: It is a privilege for me to pay tribute to this magnificent presentation and to the outstanding leader in the new field of surgery of shunting operations, and I cannot express this too strongly. There is one matter I want to mention, that is, the very interesting opportunity for studying the physiology of the patient with the shunting operation; whether they be cardiovascular, or whether they be thoracic or abdominal. It is a new field, one in which the disarranged physiology, in many instances total disability, is altered immediately by the shunting procedure, and I am sure that in the future this field will be explored extensively; but we shall always look back, those who have seen this, to this very remarkable presentation today.

DR. CLAUDE S. BECK, Cleveland, Ohio: I should like to congratulate Doctor Blalock and Doctor Taussig on this work. I have been trying to think of something in the surgical literature that might be related to this operation. The only suggestion that has any similarity to this operation was published by Jeger.* He proposed an operation for aortic stenosis consisting of anastomosis of the severed proximal end of the innominate artery to the cavity of the left ventricle, using a segment of jugular vein to connect these two structures. He also proposed an operation for mitral stenosis consisting of anastomosis of the distal end of a severed pulmonary vein to the cavity of the left ventricle using a segment of jugular vein to connect these two structures. These proposals were not applied to patients. The Blalock-Taussig operation is original in its conception. It was worked out in the experimental laboratory and, finally, it was applied to patients. The operation does not cure this cardiac abnormality. The circulation is not restored to normal. It provides definite benefit. I think it is one of the nicest contributions to surgery made in my lifetime.

Cardiovascular disease, in general, is responsible for about one death in three. This is the most important group of diseases that the physician treats, and yet the physician who treats diseases of the heart and blood vessels seldom if ever sees these organs in the living patient. We know that direct vision and direct manipulation can contribute to knowledge and understanding such as cannot be accomplished by any of the indirect methods of approach. I believe that progress in this field will be made by the direct approach to these structures. The Blalock-Taussig operation is based upon direct approach. There are funds available for cardiovascular research, and I hope that the internists who have charge of these funds will not forget that the direct surgical approach has something to offer and that surgical exploration should be encouraged.

DR. ELLIOTT C. CUTLER, Boston, Mass.: I rise to add my congratulations to the authors of the present paper. About 22 years ago, in a rather bungling fashion, I presented a direct attack upon the stenosed mitral valve. In the intervening time a great many signposts have been laid down making cardiac surgery far more safe than it was in those days. I have watched the work of Robert Gross, who first successfully accomplished the ligation of the patent ductus arteriosus. This new procedure in the field of cardiac surgery for children with other congenital lesions offers great stimulation to those who work in the field of cardiac surgery, and we are indebted to Doctor Blalock for his magnificent contribution.

*Jeger, Ernst: Die Chirurgie der Blutgefässe und des Herzens, Berlin, Hirschwald, 1913.

Dr. Rudolph Matas, New Orleans, La.: No one who has kept in touch with the marvelous progress of cardiac surgery and heard Doctor Blalock's account of his latest contribution on pulmonary stenosis and atresia can doubt that a new and unique chapter in the surgery of congenital cardiac defects has materialized. What a few years ago were fantastic speculations of laboratory workers have now become actual living and working realities. It would now seem plain that on the basis of the advances already accomplished, the surgery of the intrathoracic cardiovascular defects should be divided into (1) operations for the cure of the teratologic or congenital defects or deformities, such as patent ductus arteriosus, coarctation of the aorta and stenosis or atresia of the pulmonary artery, in which the names of Monro, Gross, Crafoord and Blalock should remain inscribed as those of pioneer founders and inspirers. In a second group, much larger and older, we should include the operations for acquired postnatal cardiovascular diseases and defects that are amenable to surgery, such as pulmonary embolectomy, cardiorraphies for traumatisms, extraction of foreign bodies, concretio or constrictio pericardi, valvulotomies for mitral and aortic stenosis, surgical treatment of coronary disease by the various methods of improving the coronary circulation, *etc.*, the excision of aneurysms from the aorta and heart itself, and still other recent achievements for acquired or pathogenic cardiac defects, the treatment of which has crowded the pages of contemporary history with the names of surgeons whose achievements here and abroad make us proud of our Science and of our Art.

Doctor Blalock's experience and magnificent success in the surgical cure of pulmonary and aortic congenital strictures are very striking from the purely technical point of view alone; his fine, finished needle work in establishing lateral and circular anastomoses between the aortic and pulmonary branches is a bit of artistry that undoubtedly contributes to the success of his work. It is impressive to note how the children who are disabled by their congenital cardiac defects sustain and survive the operations so much better than the normal dogs operated upon with the same care and technic in the experimental laboratory. It is also impressive to note how effectively the collateral circulation is spontaneously developed in the stenotic child, whether of pulmonary or aortic type. The difference in favor of the child being that in the child the collateral circulation has had a chance to adapt itself to its obstructive defect while in the dog it has not. It is also impressive to note that in these defective children the great arteries, aorta, innominate, subclavians, axillaries, can be ligated and divided and transplanted with an impunity inconceivable in normal children and adults. The carotid alone, seemingly resents interference with its function, by exhibiting secondary brain complications which spoil the results of operation that would otherwise be successful in the other arteries. The success of the work of Doctors Blalock and Taussig will undoubtedly give a great impetus to the surgery of cardiovascular teratology; and Doctor Taussig's noted skill in the differential diagnosis of these congenital defects will create a new interest in pediatricians and cardiologists which will soon be reflected in the rising statistics of the new surgery.

Dr. Emile Holman, San Francisco, Calif.: I should like to report our experience in two attempts. After operating upon 15 dogs and succeeding in half of them, we thought we were equipped to do the operation according to Doctor Blalock's technic. The first patient was 18 months old, had a hemoglobin of 182 per cent, and syrupy blood. The distance between the subclavian vessel and the pulmonary artery was so long that after we had anastomosed them there was an acute angle which interfered with proper flow. The baby expired the next day. In this case we were confronted with a remarkable collateral circulation over the mediastinum. We also noted after operation that this baby had a completely lifeless arm. We had to divide many vessels to get enough length of artery for anastomosis. In the next attempt, a five-year-old child, we avoided the subclavian artery, made an incision in the neck where

the common carotid was divided and brought down to the pulmonary artery. She has done fairly well. On the fifth day there developed hemiplegia on the left side, which was complete, and was interpreted as an embolic lesion in the internal capsule rather than thrombosis of the vessel we had divided. This has gradually improved and there is only a small residual weakness in the left arm. Again, in this second instance, the blood was exceedingly thick, and I would like to have Doctor Blalock tell us what he does to improve the condition of the blood both before and after operation.

May I, too, express my admiration for this brilliantly conceived surgical procedure, which is both breath-giving and breath-taking.

DR. ALFRED BLALOCK, Baltimore, Md. (closing): I wish to thank Doctors Whipple, Beck, Cutler, Matas and Holman. I would like to echo what Doctor Matas said about Doctor Cutler. He certainly has had a great deal to do with paving the way for subsequent advances that have been made.

Doctor Matas spoke of collateral circulation. It is quite true that in some instances all the blood to the lung goes through collateral vessels; in patients with atresia the bronchial vessels are enlarged and other vessels also contribute in carrying blood to the lung.

It is true, as Doctor Holman said, that the blood in practically all these individuals is thick; the red count may be eight, ten or 12 million; hematocrit readings as high as 95 per cent. I do not think anything should be done about that preoperatively. If a great deal of blood is lost during operation I am confident that no blood should be removed after operation, but if the operation is bloodless, to the extent that only a little is lost, we usually remove blood at the completion of the operation. We have had no difficulty with the arm on the side on which we have ligated the subclavian artery, and we have had about 90 such patients. On the other hand, we have had patients who developed cerebral ischemia or thrombosis, and I think most deaths are on that basis. We had several patients who developed weakness on the opposite side of the body, but in all those who survived, it has either cleared completely or is clearing.

Regarding the use of the carotid, it is the easiest vessel to use, but I think one should employ it only in exceptional circumstances, because if the subclavian is not big enough one should choose the biggest vessel available, the innominate. The carotid can be approached through the chest, and it is not necessary to expose it in the neck.

I want you to realize that all these operations have been undertaken in a relatively short period of time. We can make no predictions as to the condition of these patients some years hence.

I would like to acknowledge the important part Dr. Helen Taussig has played in this work, also the important rôles of Dr. Austin Lamont and Dr. Merel Harmel, who anesthetized the patients.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Manager Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.

ARTERIAL REPAIR IN THE TREATMENT OF ANEURYSMS AND ARTERIOVENOUS FISTULAE*

A REPORT OF EIGHTEEN SUCCESSFUL RESTORATIONS

LT. COL. NORMAN E. FREEMAN, M.C.†

SURGICAL SERVICE, DE WITT GENERAL HOSPITAL

AUBURN, CALIFORNIA

THE INCIDENCE OF GANGRENE due to acute ischemia following operations on aneurysms and arteriovenous fistulae is rare. Not a single instance occurred in 100 cases operated upon at DeWitt General Hospital. There was but one case in the entire series of patients in the three Vascular Centers of the U. S. Army. This splendid record is probably due both to the policy of waiting a sufficient length of time for the development of collateral circulation and to the perfection of surgical technic in order to spare the important collaterals. In addition, prophylactic sympathectomy may have helped practically to abolish gangrene after operations on arterial lesions.

Although there is sufficient circulation to care for the metabolic needs of the tissues at rest, interruption of the major artery to a limb may lead to persistent symptoms of impaired circulation. Makins[1] has emphasized the degree of disability which frequently ensues. Bigger[2] has reported that "in the patients in whom a main vessel was resected for arteriovenous fistula there was no instance of serious acute circulatory difficulty, but all of them have evidence of persistent circulatory deficiency." Because of residual symptoms of inadequate circulation following excision of aneurysms and arteriovenous fistulae sympathectomy was subsequently performed in 29 patients at one of the Vascular Centers. Although improvement was noted in the cases there was generally some residual impairment of function.

Restoration of the circulation through the damaged artery as the ideal method of treatment was recommended by Matas.[3] In the treatment of arterial aneurysms he suggested either restorative aneurysmorrhaphy in cases where the defect in the arterial wall was small or the reconstructive operation in the presence of large defects. Bickham[4] subsequently applied the Matas technic of intravascular repair to the treatment of arteriovenous fistulae. He was the first to suggest the transvenous closure of the defect in the arterial wall with preservation of the continuity of both artery and vein.

Preservation of the artery is not without its hazards. Even though the arterial repair is successful, the possibility of subsequent formation of a false aneurysm, especially in the presence of degenerated arterial wall, has been held to contraindicate the use of this technic. Reid[5] has stated "the development of an abundant collateral blood supply makes the operation unnecessary. It is doubtful if the badly degenerated artery should be restored to normal function." Bigger[2] also has emphasized the point that "the most important contra-

*Read before the American Surgical Association, April 2-4, 1946, Hot Springs, Virginia.

† From Dept. Surgery, University of California Medical School, San Francisco, Calif.

indication to arterial suture is calcification of the wall of the artery in the area to be sutured." Complications from recurrence of aneurysms following restoration of the continuity of the artery have been reported by Bigger,[2] Reid,[6] and Pemberton and Black.[7] Objection to the transvenous method of closure is based on the fact that an additional opening or weak point in the arterial wall may be overlooked. Reid and McGuire[8] have reported one example of this nature, and Holman[9] has observed another. On several occasions we have noted that both the accompanying veins communicated with the artery.

A final objection to attempting arterial repair lies in the technical difficulties. Matas,[10] in commenting on the case which he reported in which longitudinal suture of both femoral artery and vein were successfully employed, terms the procedure the "ideal method which is usually practicable only in very recent injuries in which adhesions are not so dense as to preclude mobilization of the vessels." In discussing the transvenous repair, Holman[11] remarks that it depends upon the "ability to control completely all bleeding, either by a tourniquet proximal to the lesion, or by numerous well-placed bulldog arterial clamps."

Despite these objections to arterial repair an attempt was made to restore the continuity of the artery in 23 cases of aneurysms and arteriovenous fistulae on the Vascular Surgical Section at DeWitt General Hospital between June and November 1945. During this period 67 patients with arterial injuries were subjected to operations. Repair was thus attempted in just over one-third of the patients. Success of the repair was demonstrable either by arteriography or by the presence of normal arterial pulsations distal to the lesion in 18 of the 23 cases. The only complications which could be ascribed to the attempted repair were the possible recurrence of an arterial aneurysm in one patient and the recurrence of an arteriovenous fistula in another case after transvenous suture. Subsequent excision of the fistula in the second case was followed by recovery. Table I summarizes the data on the various technics of arterial repair which were employed.

TABLE I

	Number of Cases	Successful Repair	Failure	Recurrence
Longitudinal suture	2	2	0	0
Transvenous suture	2	0	1	1
End-to-end anastomosis	2	1	1	0
Transverse suture	17	15	1	1
Total	23	18	3	2

A summary of the various locations in which arterial repair was successful is given in Table II.

TABLE II

Common carotid	3	Superficial femoral	4
Subclavian	1	Popliteal	7
Brachial	1	Posterior tibial	1
Abdominal aorta	1		

Longitudinal suture of the defect in the wall of the vein was performed on 18 occasions. In six of these patients the patency of the vein was subse-

quently demonstrated by venography. Obstruction was shown roentgenographically in six others and the result was not determined in the remaining patients.

LONGITUDINAL SUTURE

Longitudinal suture was first used in the repair of a femoral artery by Postempski[12] in 1886. This method of suture, which was advocated by Matas[13] in his reparative aneurysmorrhaphy, has been generally used in arterial repair. The arteries of two patients in this series were repaired by this technic.

CLINICAL EXPERIENCES

Case 1.—This 23-year-old male was wounded by shell fragments on November 21, 1944. Approximately two weeks later a pulsating mass was discovered on the anterior aspect of the right thigh. This mass increased in size for a period of time, but then remained stationary.

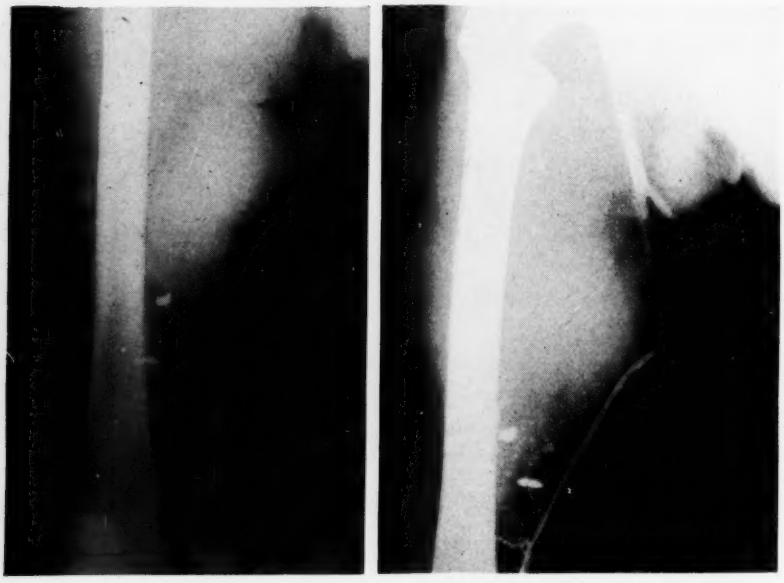


FIG. 1 FIG. 2

FIG. 1.—Preoperative arteriogram. Case 1. Large aneurysm with arteriovenous fistula of superficial femoral vessels.
FIG. 2.—Preoperative phlebogram. Case 1.

At the time of admission, physical examination disclosed the presence of a large tumor on the anteromedial aspect of the right thigh. A loud, continuous bruit could be heard over it. An arteriogram (Fig. 1), taken on February 9, 1945, showed a large arteriovenous aneurysm, which measured 13 x 8.5 cm. in diameter, involving the superficial femoral artery and vein. A phlebogram (Fig. 2), taken on March 2, 1945, demonstrated displacement of the saphenous vein to the medial side of the thigh. After allowing sufficient time for the development of collaterial circulation, he was operated upon June 28, 1945.

Operation: Under continuous spinal anesthesia, an incision was made over Hunter's canal above the aneurysm, and the dilated superficial femoral artery was encircled with rubber tubing. The incision was then carried down the thigh, over the aneurysmal sac, and the sartorius muscle was reflected medially to expose the superficial femoral artery and vein below the sac. The artery in this position was again encircled by rubber tubing. No

attempt was made to control the blood flow through the femoral vein. The artery was then dissected free from the aneurysmal sac and venous bleeding from the opening into the sac was controlled by digital pressure. The defect in the arterial wall measured approximately 1.5 cm. in length. It was closed with a continuous stitch using No. 000 silk on an atraumatic needle. During this procedure, the lumen of the vessel was irrigated with normal salt solution. After completion of the suture, the lower and then the upper rubber tubes were released. Good expansile pulsation across the suture line was observed. The sac was then widely opened and bleeding from the two orifices of the femoral vein was controlled by digital pressure until the ends could be dissected free from the sac and individually ligated. No effort was made to remove the sac. A rubber tissue drain was brought out from the lower end of the wound and the wound was then closed in layers. Following operation, the circulation to the foot and leg appeared to be excellent. An arteriogram (Fig. 3), taken on July 27, 1945, demonstrated the patency of the superficial femoral artery, although the lumen was considerably diminished at the point where the defect had been repaired.

FIG. 3.—Arteriogram. Case 1. After longitudinal repair of femoral artery.

Although pulsations of the peripheral arteries were normal, oscillometry four months later showed that there was still some impairment of circulation. Seven months after operation, the patient still complained of aching in the leg after walking six blocks.

Case 2.—This 23-year-old male was wounded in the right side of the neck, February 13, 1945, by a shell fragment. Immediately after injury, he noted hoarseness of his voice. Débridement was performed, followed by secondary closure of the wound. A few hours after his injury, he noted a thrill in the region of the wound. This condition, in addition to a slight ptosis of the right eyelid, persisted up to the time of admission. Physical examination at that time showed the classical findings of an arteriovenous aneurysm involving the right side of the neck just about the clavicle. In addition, laryngoscopy showed paralysis of the right vocal cord. Pressure upon the aneurysm caused a paroxysm of coughing. The bruit of the aneurysm could be made to disappear upon pressure over the common carotid artery behind the clavicle. This procedure did not produce any symptoms of cerebral ischemia.

Operation.—August 2, 1945: Under intratrachial nitrous oxide-ether-oxygen anesthesia, a transverse incision was made above the right clavicle. The muscles were divided close to their insertion and the greatly dilated internal jugular vein was exposed. The inferior thyroid vein was divided and the common carotid artery dissected free. This artery appeared to be about normal in size. It was surrounded by a piece of rubber tubing. Compression of the common carotid artery did not entirely obliterate the bruit heard over the fistula. Dissection was, therefore, carried above the fistula and the common carotid artery was isolated and surrounded by a second piece of rubber tubing. Compression of the artery both above and below the fistula reduced the bruit, but did not completely abolish it. Digital palpation revealed the presence of another large artery lying beneath the fascia lateral to the jugular vein. This artery, which proved to be the inferior thyroid, was divided above and below the fistula. Following this procedure, no further bruit was audible when the contributory vessels were compressed. The jugular vein, accordingly, was ligated above and below the fistula and the carotid artery was dissected away from the aneurysm. The defect in the wall of the carotid was closed with a longitudinal running stitch and the segments of the jugular vein, with the aneurysm which lay posterior to it, was excised. Good pulsation was present in the distal part of the carotid artery one hour after suture. The wound was closed in layers without drainage. Convalescence was uneventful and the patient was discharged four weeks

after operation. At this time, pulsation of the right temporal artery was normal. This pulsation was not affected by compression of the left carotid artery, but it was obliterated when compression was made on the right side of the neck. Six months later, he reported that his only residual symptoms were hoarseness and some drooping of the right eyelid. There was no evidence of recurrence of the aneurysm and he was able to exercise as much as he desired.

COMMENT.—Longitudinal closure of the defect in the arterial wall was successfully accomplished in two cases. Where the opening is small, distortion of the arterial wall by suture is not marked. However, in larger defects, the resultant distortion of the normal contour may curtail the volume flow of blood through the restored artery. Reënforcement of the suture line by the use of a part of the sac wall, may reduce still further the caliber of the vessel. Waugh[14] has reported a case in which the diameter of the vessel was reduced by one-half by this procedure. The maintenance of a full volume flow of blood past the suture line seems to be of importance in preventing subsequent thrombosis at this site.

TRANSVENOUS SUTURE

Transvenous suture of the fistulous opening between the artery and vein was first suggested by Bickham.[4] This operation has been referred to as the "Matas-Bickham" procedure. The suture is introduced through the scar tissue between the vessels into the lumen of the vein and the opening is closed with a running stitch. The suture is then tied after being passed out through the vein wall so that no suture material is left free in the lumen of the vein. The incision in the wall of the vein is then closed by a running stitch. This technic was used in two cases in the present series.

CLINICAL EXPERIENCES

Case 3.—This 28-year-old male was wounded in the left knee by a rifle bullet on March 13, 1945. There was considerable hemorrhage which recurred on several occasions. He was admitted to this Vascular Center on April 6, 1945. At that time, there was considerable swelling of the left calf and ankle and a pulsating mass in the popliteal space over which was observed the characteristic thrill and bruit of an arteriovenous fistula. The ankle pulses were absent on the left side and the oscillations were markedly decreased. Arteriogram (Fig. 4), April 17, 1945, revealed an arteriovenous fistula at the level of the head of the fibula. Dye was present in the veins on both sides of the artery. The significance of this observation was not realized until later. Lumbar sympathectomy was performed, August 13, 1945, with improvement in the collateral time and circulation to the left foot.

Operation—September 13, 1945: Under continuous spinal anesthesia, the vessels were exposed between the heads of the gastrocnemius muscle in the lower portion of the popliteal space. The popliteal artery lay between two veins in this location. The veins were not separated from the artery, but the entire vascular bundle was surrounded by a piece of rubber tubing both above and below the fistula. Each vein, in turn, was opened and the communication with the artery was visualized. On each side the opening measured approximately 7 mm. in length. It was closed longitudinally according to the Matas-Bickham technic, using a running stitch of No. 000 silk on an atraumatic needle. The sutures were tied outside of the vein. Release of the upper tube now demonstrated a small amount of bleeding of the artery into one of the veins and two additional stitches were taken in the suture line within this vein. At the conclusion of this procedure, there was no further bleeding from

the artery into the vein. The incision on the posterior surface of the vein was then closed with a running longitudinal stitch and all the blood vessels were released. Auscultation now revealed a very faint bruit in the region of the fistula. However, further dissection failed to disclose the source of this faint continuous bruit. Accordingly, it was assumed to be due to the turbulence of the blood stream as it passed over the suture lines. The wound was closed without drainage. After operation, the posterior tibial pulse was excellent and oscillometry showed a considerable improvement in the circulation to the left leg and foot. However, auscultation revealed the persistence of a faint continuous bruit with systolic accentuation. The patient was then sent on a convalescent furlough. Upon his return, he stated that while walking he had suddenly felt something snap in the region of the old aneurysm and upon palpation had noticed a recurrence of the thrill. When he was reëxamined, a loud continuous bruit was audible.

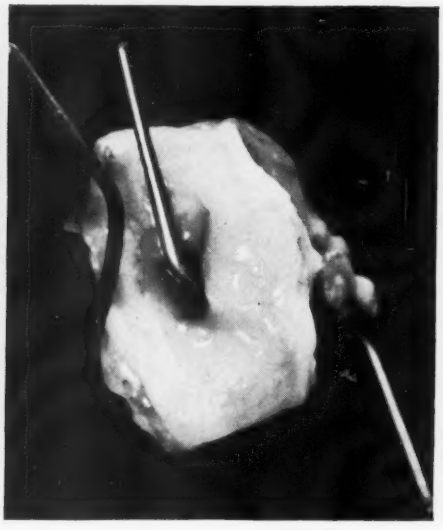


FIG. 4 FIG. 5

FIG. 4.—Preoperative arteriogram. Case 3. Reflux of dye into both popliteal veins.

FIG. 5.—Excised fistula. Case 3. Lower wire indicates third communication overlooked at previous operation. Upper wire placed through recurrent fistula.

Second Operation.—November 17, 1945: A longitudinal incision was made posterior to the head of the fibula extending upward medial to the biceps tendon. The peroneal nerve was exposed and retracted laterally and the lateral head of the gastrocnemius muscle was retracted posteriorly to expose the popliteal vessels as they passed through the ring of the soleus muscle. An aneurysm, which measured 2 cm. in diameter, was present at this point. The artery above the aneurysm was freed up and encircled by a piece of rubber tubing. Compression of this tubing now obliterated all bruit in the aneurysm. The head of the soleus muscle was then divided close to its attachment to the head of the fibula and retracted posteriorly, together with its nerve and blood supply. The popliteal artery was thus exposed below the aneurysm. At this point there was a moderately dilated vein overlying the artery. It was possible to observe the turbulent flow of mixed arterial and venous blood in this vein. This vein was divided and ligated in order to expose the popliteal artery below the fistula. The artery was again encircled by a piece of rubber tubing. The proximal and distal arteries were divided and ligated and the component veins were treated in a similar manner and

the aneurysm was excised. Upon examination of the specimen, there were two openings from the artery—one, a small one, shown by the lower pointer (Fig. 5) where a communication with a small vein had apparently been overlooked at the original operation. The larger opening was due to a rupture of the artery into the vein at the point where it had been sutured at the original operation. The patient recovered from this operation without complications but the circulation to the left foot was definitely decreased. Oscillations at the ankle were less than one-quarter of those on the normal side. In spite of this fact, the circulation was fairly well maintained so that the patient was able to walk for as much as three blocks before developing signs of intermittent claudication.

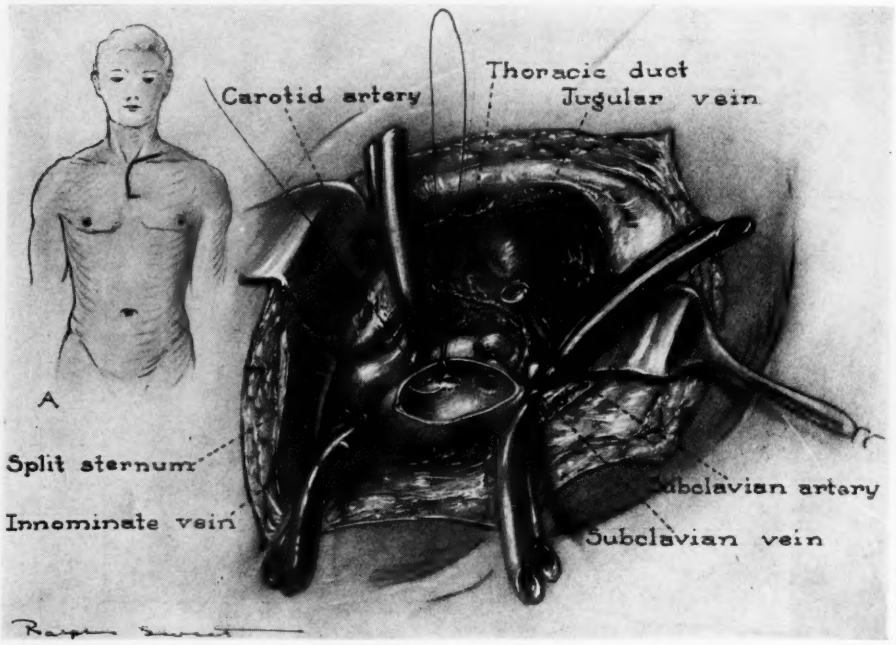


FIG. 6.—Transvenous repair of fistula involving left subclavian artery and innominate vein. Case 4.

Case 4.—This 24-year-old male was struck by shell fragment just above the left clavicle on July 29, 1944. After the initial débridement, it was noted that his left radial pulse was absent although, subsequently, it returned. From the time of the injury, the patient believed that the temperature of the left upper extremity was lower than that on the right side. Except for difficulty in articulation for the first few days after injury, he had no complaints. However, a loud continuous bruit was audible over the left sternoclavicular joint. He was admitted to the Vascular Center in October, 1944. Venous pressure was found to be 16.4 cm. of water on the left side and 13.4 cm. on the right. The circulation time was 20 seconds on the left and 9 seconds on the right. Attempts to compress the aneurysm by pressure in the supraclavicular region were unsuccessful. In spite of the fact that the aneurysm was close to the heart, no evidence of cardiac enlargement was noted during a long period of observation.

Operation.—September 10, 1945: Under endotracheal, nitrous oxide-ether-oxygen anesthesia, a transverse supraclavicular incision was made on the left side, extending down over the manubrium to the second rib, thence lateralward to the costochondral junction. (Fig. 6.) The muscles attached to the clavicle and sternum were divided close to their

insertions. The internal jugular vein was thus exposed and the turbulent mixing of arterial and venous blood could be observed. Pressure on the junction of the internal jugular and subclavian veins stopped the bruit in the fistula. The common carotid artery on the left side was then exposed. Its pulsation was feeble and the wall was thick. Occlusion of this artery, however, did not prevent the thrill in the aneurysm. Further dissection revealed a greatly dilated innominate vein. It was impossible to expose this vein adequately without opening the thorax. Accordingly, the medial 2.5 inches of the left clavicle were resected subperiostially, leaving the sternoclavicular articulation intact. The tissues were then freed beneath the sternum in the midline and the manubrium was split to the upper border of the second rib, and then cut transversely at this level. The left half of the manubrium was then readily retracted lateralward to expose the thymus lying on the large dilated innominate vein. Some branches of this vein were ligated and divided. The innominate vein and left carotid artery were retracted medially to expose the left subclavian artery as it arose from the arch of the aorta. The subclavian artery was considerably larger than the carotid and the walls were thin. The pressure within the artery seemed to be low. It was encircled by a fine catheter which was fitted to a Bethune tourniquet. Compression of the subclavian artery at the arch of the aorta obliterated the thrill in the aneurysm. Although the bruit ceased abruptly as soon as the subclavian artery was compressed, within a short interval a faint bruit was again audible, probably indicative of collateral circulation. The internal jugular vein was then divided above its junction with the subclavian. Dissection on the medial side of the internal jugular vein revealed a large lymphatic duct which entered the junction of the jugular with the subclavian. The phrenic nerve was retracted medially and the scalenus anticus muscle was divided in order to expose the second portion of the subclavian artery. The internal mammary artery was carefully preserved but the costocervical and the thyrocervical trunks were ligated. The subclavian artery distal to the fistula was markedly reduced in caliber. It was surrounded in this location by a piece of rubber tubing. The first portion of the subclavian artery just proximal to the origin of the vertebral artery was then exposed and surrounded by a second piece of rubber tubing. With the subclavian artery compressed just proximal to the vertebral artery and distal to the fistula and with the vertebral artery compressed, the bruit was abolished. The innominate vein no longer filled with arterial blood. The subclavian and innominate veins were then occluded by additional pieces of rubber tubing and the innominate vein was opened on its anterior aspect close to the junction of the jugular with the subclavian vein. The vein was flushed out with normal saline. It was possible to see an aperture which measured approximately 1 cm. in length lying over the subclavian artery. (Fig. 6.) The opening from the artery into the vein was sutured from within the vein by the Matas-Bickham technic, using No. 000 silk. The suture was started from outside the vessel, passing into the lumen and then after closing the opening with a running stitch the suture was doubled back on itself and the ends brought outside of the vein to be tied at the starting point. After this suture had been completed, the distal artery, the vertebral, and then the proximal artery, in turn, were released. There was some slight bleeding into the vein which was controlled by an additional stitch. The incision on the anteromedial surface of the innominate vein was then closed with a running longitudinal stitch. The two halves of the manubrium were approximated with two steel wire sutures and the muscles and superficial tissues closed in layers.

The patient developed a wound infection which necessitated incision and drainage two weeks after the original operation, but satisfactory recovery then took place. Although there were no signs of circulatory insufficiency of the left upper extremity, the radial pulse continued to be markedly diminished and the oscillations were reduced. Six weeks after operation, a phlebogram demonstrated the patency of the left innominate vein. Five months after operation the patient reported that he had noticed no recurrence of the fistula. However, he was short of breath and experienced precordial pain on exercise. Since there was no cardiac enlargement even before operation it is unlikely that the fistula could have caused serious cardiac disturbance.

COMMENT.—Transvenous suture, although it has been considered a logical procedure, has two decided drawbacks. Since the artery need not be fully mobilized, a second and even a third communication may be overlooked. This complication has been reported by Reid and McGuire[8] and accounted for the persistence of the arteriovenous fistula in Case 3 of this series. The second objection is the fact that the arterial wall may be weakened or defective either close to the fistula or at some other point. Without careful scrutiny of the arterial wall both from within and from without, this damaged area may be overlooked. Subsequent rupture with the formation of an aneurysm may result.

FIG. 7.—Preoperative arteriogram. Case 5. Superficial femoral arteriovenous aneurysm.

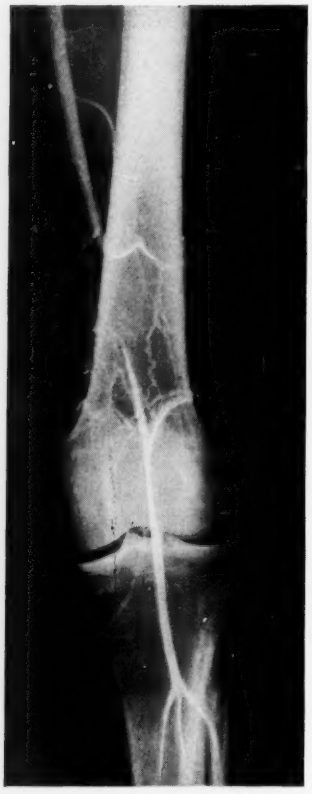


FIG. 8.—Postoperative arteriogram. Case 5. Failure of end-to-end anastomosis. Excellent collateral circulation.

END-TO-END ANASTOMOSIS

The first successful end-to-end anastomosis of an artery was reported by Murphy[15] in 1896. Since that time numerous reports of this procedure have been made, especially following the work of Carrell.[16] Few demonstrably successful cases have been reported. This technic has been employed in two cases in the present series.

CLINICAL EXPERIENCES

Case 5.—This 25-year-old male was wounded in the left thigh on January 15, 1945. He developed signs of an arteriovenous fistula in the lower part of the thigh. At the time of admission to the Vascular Center, July 15, 1945, he showed characteristic signs of an arteriovenous fistula involving the lower portion of the femoral vessels. Arteriogram (Fig. 7), July 20, 1945, showed an aneurysmal sac lying to the medial side of the femoral artery, with a communication into the lower femoral and popliteal veins. Sympathectomy was performed on July 30, 1945. After this operation, the collateral circulation seemed to be adequate.

Operation.—August 23, 1945: A longitudinal incision was made over the lower part of the adductor canal. The femoral artery was exposed above and below the fistula. The aneurysm was present on the lateral side of the artery. With digital compression of the veins, the artery was dissected free from the aneurysm and from the vein. The opening into the vein was closed with a longitudinal running stitch. Two large defects were present in the arterial wall. Because so little sound arterial wall remained, a resection of the damaged portion was performed with end-to-end anastomosis. After release of the rubber tubing, expansile pulsation was transmitted across the suture line. The wound was closed without drainage. After operation, the peripheral pulses were good and oscillations at the left ankle were three units in comparison to a reading of five units on the normal side. With the excellent peripheral pulses and practically normal circulation, it was believed that a successful repair had been accomplished. However, an arteriogram, taken six weeks after the operation (Fig. 8), showed that the segment had been completely obliterated and that the circulation was carried on entirely by means of collateral vessels.

Case 6.—This 28-year-old male was wounded by a rifle bullet in the left thigh on February 28, 1945. The wound of entrance was two inches below Poupart's ligament. After débridement in the forward area, an arteriovenous fistula was discovered in this region. He was admitted to the Vascular Center on July 1, 1945. Arteriogram, September 7, 1945, showed a communication between the femoral vessels just distal to the profunda.

Operation.—October 1, 1945: A semilunar incision was made over the upper portion of the thigh with its center at the wound of entrance. The common femoral artery was exposed below Poupart's ligament. It was greatly dilated with thin walls. This artery was surrounded by a piece of rubber tubing. Compression of this tubing now obliterated the thrill in the arteriovenous fistula although a slight bruit was still audible. The artery was again exposed below the profunda femoris, but further auscultation revealed that the aneurysm involved the superficial femoral artery below this second temporary ligature. Accordingly, the dissection was carried further down the thigh by retracting the sartorius muscle medially and the femoral artery was exposed in Hunter's canal. With both the proximal and the distal artery occluded, the bruit was completely abolished. The artery was separated from the vein by sharp dissection. Some brisk venous bleeding was controlled by digital pressure until the femoral vein could be sutured. It was found that the wall of the femoral artery had been destroyed over a very wide range and there were two perforations in it, one on the lateral and one on the medial side. Accordingly, the artery was divided and the damaged portion excised. The artery had to be dissected free for a distance of two inches below and upward to the point at which the profunda femoris vessel left it, in order to obtain sufficient relaxation to permit suture. An end-to-end anastomosis was then performed, using a continuous running stitch of No. 000 silk. After release of the rubber tubing there was some bleeding which was controlled with additional stitches. At the conclusion of the operation, there was good pulsation transmitted across the suture line. The wound was closed without drainage.

Convalescence was uneventful and the peripheral pulses remained excellent. Oscillometry showed no diminution on the side of operation. Arteriogram and phlebogram, two months after operation, demonstrated patency of the vessels. The patient reported five months after operation that he had been working steadily but that he had pain in the lower part of

the leg when standing for a long time or walking very far. There was no swelling and the circulation was good.

COMMENT.—End-to-end anastomosis was successful in one of the two cases in this series in which it was attempted. Obliteration occurred in the first case. The patient recovered, however, since the collateral circulation was abundant, and little vascular insufficiency resulted.

TRANSVERSE SUTURE

Transverse suture of the laceration in the arterial wall has been recommended by Learmouth[17] if the wound does not involve more than one-third of the circumference. It has been our experience that transverse suture is

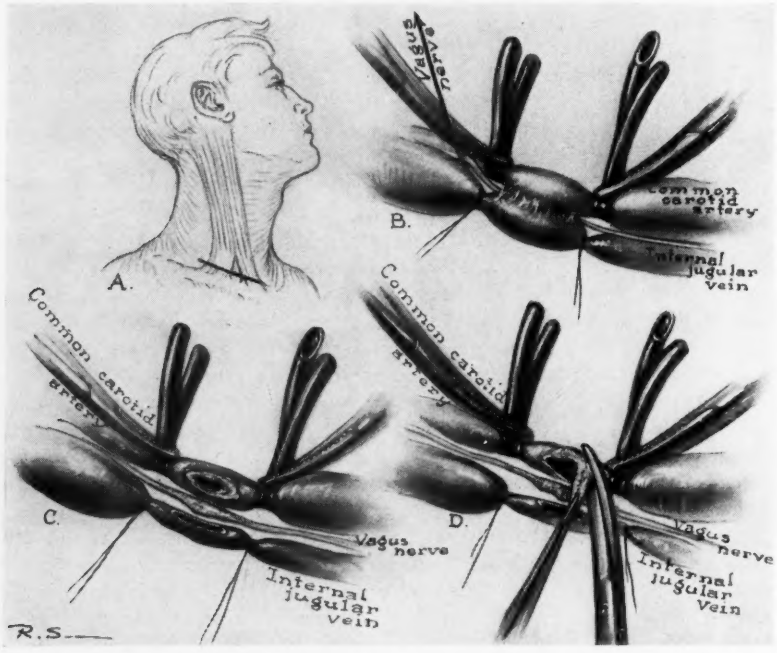


FIG. 9.—Carotid-jugular arteriovenous aneurysm. (A) Position of incision. (B) Circulation through component vessels controlled. (C) Fistula divided. (D) Excision of damaged portion of arterial wall.

possible even though more than three-fifths of the vessel wall is lacking. Control of the circulation through the artery above and below the fistula is first obtained by the use of sections of rubber tubing. As shown in Figure 9-B the rubber tubing is clamped close to the vessel wall by means of fine curved hemostats. The use of rubber tubing prevents damage to the arterial wall and the hemostats facilitate manipulation of the artery during the dissection and subsequent repair. After control of the major arterial supply has been obtained, auscultation at the site of the fistula by means of a sterile stethescope is essential in order to exclude additional arterial components. Persistence of bruit indicates that some other artery is still connected with the fistula. When the completeness of the arterial control has been verified the vein is

encircled above and below the fistula with heavy silk thread. With the component vessels controlled the artery is then dissected free. After irrigation of the lumen with normal saline the entire arterial wall is inspected both from within and from without. The damaged arterial wall is then excised (Fig. 9-D) in an elliptical fashion. Relaxation can be obtained by approximating the vessel on either side of the defect with the aid of the rubber tubing used to control the circulation. Especially in the presence of an arteriovenous fistula,

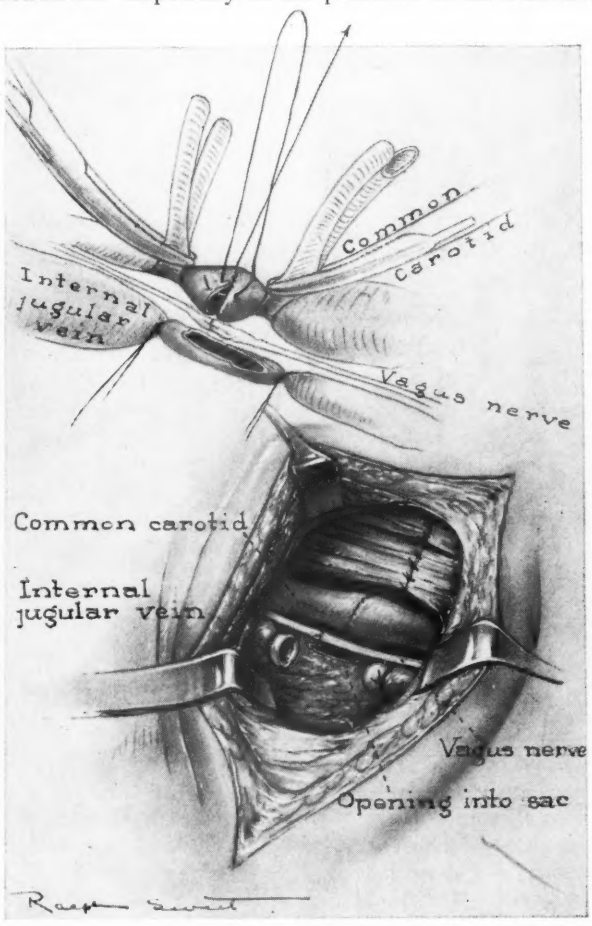


FIG. 10.—Transverse repair of defect in carotid artery. Insertion of running stitch through entire thickness of arterial wall. Repair completed.

sufficient dilatation with elongation of the afferent artery has taken place to permit this approximation. Additional relaxation can be obtained by dissection of the artery up to the point of origin of the nearest branch. However, no important collateral vessel should be sacrificed. After approximation of the edges of the arterial wall the defect is closed by a running stitch which passes through all layers (Fig. 10). It may be doubled back on itself and tied at its point of origin. We have used No. 000 silk (Deknatel) on an atraumatic

needle and have passed this suture material through sterile mineral oil. After completion of the closure, first the distal and then the proximal portion of the artery is released. Bleeding from the suture line is generally mild and stops spontaneously. Otherwise an additional stitch of No. 00000 silk may be needed. Frequently there is some distortion of the artery due to a bulge of the redundant part of the normal vessel wall opposite the line of suture. This distortion has not apparently interfered with the volume flow of blood which passes the suture line. In no case, when good expansile pulsation was observed distal to the suture line after transverse closure, did subsequent thrombosis occur.

Frequently extensive dissection would have been required in order to isolate all the venous components of an arteriovenous fistula. Under such circumstances, after complete control of the arteries had been obtained, reflux bleeding was simply controlled by digital pressure as the artery was dissected from the vein. The opening into the vein was then closed with a suture.

Transverse suture was successful in 15 of the 16 cases in which it was attempted.

CLINICAL EXPERIENCES

Case 7.—The patient, a 24-year-old male, was wounded in the neck, arms and legs by multiple mortar fragments on April 1, 1945. He developed subcutaneous emphysema of the neck which subsided spontaneously, but subsequently characteristic signs of arteriovenous fistula on the left side of the neck at the level of the thyroid cartilage were observed. These signs persisted up to the time of admission to the hospital on May 27, 1945. In addition, laryngoscopic examination showed paralysis of the left vocal cord. Three months after he was wounded, compression of the common carotid artery below the fistula produced no evidence of cerebral ischemia.

Operation.—July 23, 1945. Under local anesthesia, an oblique incision was made parallel to the skin creases at the level of the thyroid cartilage. Dissection was carried down medial to the sternomastoid muscle and the common carotid artery was isolated below the fistula. A rubber tube was placed about the artery at this point. The common carotid artery was again isolated above the fistula and treated in a similar manner. The jugular vein was greatly dilated. It was dissected free and a heavy black silk thread placed about it both above and below the fistula. The vagus nerve was then freed up to the point where it was incorporated in the scar between the carotid artery and the jugular vein. One per cent procaine was injected into the vagus nerve above the line of scar tissue. With the common carotid artery compressed both above and below the fistula, the vagus nerve was dissected free and the communication between the artery and vein was opened. The communication measured 1 cm. in diameter. The defect in the arterial wall was on the posterolateral side and, on inspection, it was noted that the media was defective in the region of the aperture. The defective portion of the wall of the common carotid artery was then excised. After relaxation of tension, the defect in the arterial wall was closed in a transverse direction by a running stitch doubled back on itself. After release of the rubber tubing, pulsation took place across the suture line. There was no evidence of narrowing of the vessel. The opening into the jugular vein was then sutured with a longitudinal running stitch. After excision of the damaged segment of the vagus nerve, the two ends were united. At the conclusion of the operation, the carotid artery was again examined. Good pulsatile flow could be demonstrated above the suture line. The wound was closed in layers without drainage.

Recovery occurred without complications. He was discharged from the hospital one month after operation. It was possible, in the postoperative period, to demonstrate the patency of the left common carotid artery by noting the fact that the temporal pulse on the

left side was unaffected by compression of the right common carotid artery, but could be obliterated by compression of the one on the left side. Six months after operation, he reported that he still was unable to work and that he could not exercise as much as he would like to because of being short-winded. There was no recurrence of the swelling in the neck. Normal voice had not yet returned.

Case 8.—This 21-year-old male sustained many wounds of the chest, abdomen, and right leg from mortar fragments on December 21, 1944. During the course of hospitalization it was discovered that he had an arteriovenous aneurysm of the right popliteal space. At the time of admission to this hospital, March 28, 1945, there was a pulsating mass in the right popliteal space with a characteristic thrill and bruit. Preoperative arteriogram, May 22, 1945, (Fig. 11), showed considerable reflux of dye into the dilated popliteal vein.

FIG. 11.—Preoperative arteriogram. Case 8. Popliteal arteriovenous fistula.

FIG. 12.—Postoperative arteriogram. Case 8. After transverse repair of popliteal artery.

The communication between the artery and the vein seemed to be at the superior level of the patella. On July 9, 1945, a lumbar sympathectomy was performed. This operation was followed by an excellent return of collateral circulation.

Operation.—August 9, 1945. Under continuous caudal anesthesia a Z-shaped incision was made with the transverse bar across the popliteal crease. The incision was deepened along the tendon of the semimembranosus muscle. Many small veins were encountered which entered the greatly dilated popliteal vein. The section of rubber tubing was placed about the entire vascular bundle including both the artery and the vein. Dissection was then carried on below the fistula and the popliteal artery was isolated and encircled by a section of rubber tubing. The popliteal vein was surrounded by heavy silk cord. Further dissection above the aneurysm resulted in separation of the artery from the vein so that each was independently controlled. With the component vessels occluded, the artery was

dissected from the vein and the communication was severed. This defect measured 1 cm. in length. The opening in the wall of the vein was closed with a running longitudinal stitch. The arterial wall was found to have been damaged to an extent of about one-half its circumference. Accordingly, a wedge-shaped portion of the lateral wall was excised and the defect closed in a transverse direction with a continuous suture of No. 000 silk placed through all coats of the vessel. Some bleeding which followed release of the occlusive rubber tubing was controlled with a suture. There was only slight reduction in the diameter of the artery at the point of suture and, after release of the rubber tubes, vigorous pulsation was noted below the suture line. At the conclusion of the operation, the posterior tibial pulse was full and bounding. The wound was closed without drainage. Postoperatively, normal pulses were present at the right ankle, and oscillometry on the right side was almost equal to that on the left. Arteriogram, taken on August 24, 1945, (Fig. 12), showed practically no distortion at the suture line. Reëxamination four months after operation disclosed a normal peripheral circulation and he reported six months after operation that he was able to walk several miles without any trouble.

Case 9.—This 22-year-old male was struck by a shell fragment, July 18, 1944, just above the right clavicle. In addition, he sustained severe wounds of both legs and the left forearm. Amputation of the left forearm was performed. After treatment in other General Hospitals, he was admitted to this hospital, March 5, 1945, with classical signs of an arteriovenous aneurysm at the base of the neck on the right side. It was difficult to obliterate the bruit by pressure above the clavicle. Despite the length of time between wounding and operation, he developed no signs of cardiac damage.

Operation.—August 20, 1945: Under endotracheal nitrous oxide-ether-oxygen anesthesia, a supraclavicular incision was made. The muscles attached to the sternum and clavicle were divided at their insertion in order to expose the internal jugular vein. Both the right and left inferior thyroid veins were divided and ligated and the deep cervical fascia was incised. The internal jugular vein was retracted laterally and dissection was carried down behind the clavicle to expose the innominate artery. This artery was surrounded by a piece of rubber tubing, fitted to a Bethune tourniquet. Occlusion of the artery caused marked decrease in the bruit over the fistula. Compression of the common carotid artery did not affect the bruit. The rubber tubing was then transferred to the subclavian artery just proximal to the origin of the vertebral. The scalenus anticus muscle was then divided, after retracting the phrenic nerve medialward, to expose the second portion of the subclavian artery. The communication appeared to involve the internal jugular vein and the subclavian artery just proximal to the origin of the thyroid axis. The jugular vein was divided and its upper portion ligated. After compression of the subclavian artery proximal and distal to the fistula, the vein was dissected free from the artery to expose a small opening approximately 0.5 cm. in diameter. This opening was closed transversely with interrupted stitches of No. 000 silk (Fig. 13). Following release of the occluding rubber tubing good pulsation was present in the artery distal to the suture line. The jugular vein was ligated close to its junction with the right subclavian and the wound was closed in layers without drainage. Convalescence was uneventful, and at the time of discharge the right radial pulse was normal.

Case 10.—This 30-year-old male sustained multiple wounds from shell fragments on February 7, 1945. While he was a patient at another hospital, he became aware of a thrill in the left popliteal space. He was admitted to the Vascular Center on May 10, 1945. At that time, examination disclosed characteristic evidence of an arteriovenous fistula involving the vessels in the left popliteal space. Arteriogram, May 25, 1945, (Fig. 14), showed considerable reflux of dye into the popliteal vein. Left lumbar sympathectomy was performed on July 30, 1945. The collateral circulation was excellent following this operation.

Operation.—August 26, 1945: Under continuous caudal anesthesia, a curved incision was made across the left popliteal space. The popliteal artery above and below the fistula was exposed and surrounded by pieces of rubber tubing, and the popliteal vein was surrounded by pieces of heavy black silk. The artery was then dissected away from the vein.

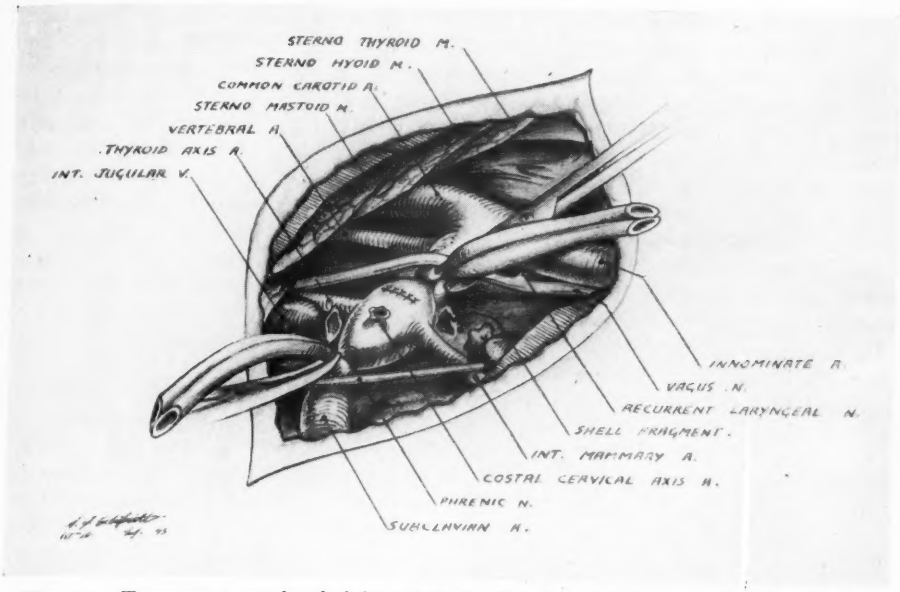


FIG. 13.—Transverse repair of right subclavian-jugular arteriovenous fistula. Case 9.

leaving a portion of the venous wall attached to the artery. After dissecting the artery away from the fistula, it was discovered that the artery communicated with two veins. The openings in both veins were closed with running sutures. The artery was then carefully irrigated with saline and rotated inward to expose the two openings. Since there was apparently normal arterial wall between the two defects, each opening was closed separately by a continuous stitch of No. 00000 silk, which was doubled back on itself. After release of the distal and proximal compression of the popliteal artery, some further bleeding took place which was controlled by an additional stitch. Normal pulsation of the popliteal artery was present below the lines of suture at the time of closure. Subsequent to operation, no disturbances of the peripheral circulation were noted. The oscillometry at the ankle was equal to that before operation. Arteriography, September 11, 1945, (Fig. 15), showed some dilitation of the artery at the line of suture. This examination was repeated on November 23 and, at that time, the distortion of the lumen of the artery was not as pronounced. Phlebogram demonstrated patency of the popliteal vein. Five months after operation, he reported that there had been no recurrence of the arteriovenous fistula, and no swelling in the region of the aneurysm. He still was unable

FIG. 14 FIG. 15

FIG. 14.—Preoperative arteriogram. Case 10. Popliteal arteriovenous fistula.

FIG. 15.—Postoperative arteriogram. Case 10. Slight dilation of popliteal artery following transverse repair.

to exercise as much as he was inclined to because of weakness and aching in both legs, associated with some muscle cramps on the left side.

Case 11.—This 21-year-old male was wounded August 28, 1944, in the right leg by numerous shell fragments. Signs of an arteriovenous fistula were noted soon afterwards in the right popliteal space. He was originally treated in another hospital for his other wounds and was then admitted to this Vascular Center on January 16, 1945. Collateral circulation was very slow to develop, and he showed considerable evidence of impairment of circulation. Right lumbar sympathectomy was performed on August 2, 1945. After this operation, the circulation was considered adequate for operation on his arteriovenous aneurysm.

Operation.—August 27, 1945. Under continuous spinal anesthesia an incision was made over the popliteal space and the popliteal artery was dissected free above the fistula. Some difficulty was experienced in isolating the popliteal artery below the fistula, due to the presence of numerous large veins draining the medial head of the gastrocnemius muscle. After isolation of the artery below the fistula, a pneumatic tourniquet, which had previously been applied about the thigh, was inflated to 200 mm. of mercury and the popliteal artery was separated from the vein. The communication measured approximately 7 mm. in diameter. A portion of the venous wall was left attached to the artery. The defect in the arterial wall was sutured in a transverse direction with a continuous silk stitch. The venous side of the communication was simply ligated. At the conclusion of this procedure there was good circulation across the suture line. However, on auscultation, it was possible to localize a bruit to a point approximately 2.5 inches below the first arteriovenous fistula. Dissection was then carried down along the posterior tibial artery, carefully preserving the branches, in order to disclose this second arteriovenous fistula. The arteries proximal and distal to the fistula were again occluded with rubber tubing, while the bleeding from the venous side was controlled by digital pressure as the artery was cut away from the fistula. A large opening, measuring approximately 1 cm. in length, was disclosed. The vein was sutured with a running stitch of silk and, although there was a fairly large gap between the two ends of the artery with destruction of more than three-fifths of its wall, a transverse closure was effected. At the conclusion of the operation, good pulsation was present below the suture line. The wound was closed in layers without drainage. In the postoperative period, whereas oscillations at the ankles had been reduced on the affected side to one-quarter of the normal, after operation, they were 50 per cent greater than those on the normal side. Arteriogram, taken three months after operation, showed that there was little distortion of the vessel at either of the sutured areas. Five months after operation he reported that he had had no return of his aneurysm and his only complaint was that the lower part of his leg became weak in case he walked too fast.

Case 12.—This 24-year-old male was wounded on March 22, 1945, by a 25 caliber bullet which passed through the popliteal space of the right side. There was no nerve damage and very little hemorrhage, but approximately two weeks after injury the patient noted the characteristic thrill of an arteriovenous aneurysm. He was admitted to this Vascular Center on April 26, 1945. Since the collateral circulation was slow to develop and his feet were cold and moist, a right lumber sympathectomy was performed on August 8, 1945. Following this operation, the collateral circulation appeared to be adequate.

Operation.—August 30, 1945: Under continuous spinal anesthesia the popliteal vessels were exposed in the midportion of the popliteal space. The popliteal artery was surrounded by a piece of rubber tubing both above the fistula and below it. The vein was similarly controlled above and below the fistula. A small aneurysmal dilitation of the artery was present on the side opposite the communication with the vein. After excision of this portion of the arterial wall and the damaged portion of the arterial wall surrounding the fistula, the defect was found to involve approximately one-half of the circumference. This defect was closed transversely with a running stitch. Considerable difficulty was encountered from bleeding at the suture line, following release of the rubber tubing, but this was controlled with additional stitches. The vein was closed in a longitudinal fashion. The wound was closed without

drainage. Two weeks after operation, oscillations on the affected side were greater than those on the normal side. Six months later he reported that he had had no recurrence of the fistula. However, he noted pain and fatigue in the calf after walking seven or eight blocks.

Case 13.—This 27-year-old male was wounded by shell fragments in the right thigh, trunk and face on January 20, 1945. During convalescence from these wounds, an arteriovenous fistula of the right femoral vessels was noted. He was admitted to this Vascular Center on May 18, 1945. Arteriogram, taken on May 20, 1945, revealed an arteriovenous fistula in the upper portion of the superficial femoral vessels on the right side and, in addition, a small aneurysm on the lateral side of the artery (Fig. 16). Because of impaired circulation, a lumbar sympathectomy was performed on August 8, 1945. After this operation there was considerable improvement in the collateral circulation.

Operation.—September 13, 1945: The superficial femoral artery was exposed in the upper third of the thigh. Rubber tubes were placed about the artery both above and below the fistula. A pneumatic tourniquet was then inflated and the artery was dissected away from the vein and from the aneurysm. The aneurysm was found to be present on the posterolateral side of the artery while the opening between the artery and the vein was on the posteromedial side. The opening into the vein was closed with a longitudinal running stitch and the pneumatic tourniquet deflated. The defect in the arterial wall measured approximately 1.5 cm. in length. The portion of the arterial wall which was damaged, including the segment between the opening into the vein and the opening into the aneurysm, was excised. Approximately three-quarters of the circumference was lacking. In order to approximate the two ends, it was necessary to free-up the artery, both above and below the fistula, for a distance of approximately 1.5 inches. No large branches were found. Because of the location of the arterial defect, the suture line was oblique rather than either transverse or longitudinal. A small amount of bleeding took place from the suture line after release of the rubber tubing, and this required an additional stitch. There was a slight distortion of the arterial wall on the opposite side from the repair. No attempt was made to remove the aneurysm. The wound was closed without drainage. Postoperative convalescence was normal. Oscillometry before operation showed a maximum of two on the right side, and seven on the left. Following repair of the femoral artery, the oscillations were three on the right side, and 3.5 on the left. Arteriography, three months after repair showed normal continuity of the superficial femoral artery (Fig. 17). A phlebogram demonstrated patency of the femoral vein. However, four months after operation he reported that he was not able to exercise as much as he desired because if he walked too much his leg became swollen below the knee. There was no recurrence of the arteriovenous fistula, and no evidence of swelling in the region of the aneurysm.

FIG. 16.—Aneurysm with arteriovenous fistula of superficial femoral artery. Case 13. Preoperative arteriogram.

Case 14.—This 19-year-old male was wounded by shell fragment in the neck, on February 18, 1945. The following day, he noted a buzzing sensation in the right side of the neck. At the time of admission to this Vascular Center, March 13, 1945, he had characteristic

signs of an arteriovenous fistula involving the vessels at the base of the neck, on the right side. In addition, there was paralysis of the right vocal cord.

Operation.—September 24, 1945. (Cf. Figs. 9 and 10.) Through a transverse supraclavicular incision, after dividing the muscles attached to the sternum and clavicle, the internal jugular vein was exposed. The inferior thyroid vein was divided and ligated, and the jugular vein retracted laterally to expose the carotid artery. A piece of rubber tubing was placed about this artery. Occlusion of this tubing obliterated the thrill but did not prevent the bruit in the arteriovenous fistula. However, when the common carotid above the fistula was also compressed by rubber tubing, all bruit was prevented. The internal jugular vein was then controlled above and below the fistula with silk ligatures and the artery was dissected from the vein. The opening from the artery into the vein measured approximately 1 cm. in length. Posterior to the vein there was a large aneurysmal sac which extended down into the superior mediastinum. A considerable portion of the venous wall was missing and, accordingly, the vein was divided and ligated. The damaged portion of the arterial wall was excised and the defect was closed in the transverse direction. Following completion of this procedure, the tubing was released and good arterial pulsation was felt distal to the suture line. The vagus nerve, which was incorporated as part of the scar tissue about the sac, was sutured after excision of the damaged portion. The wound was closed without drainage. Four months after operation he reported that, although his voice had not improved, there had been no recurrence of the aneurysm or the fistula.

FIG. 17.—Postoperative arteriogram. Case 13. After diagonal suture.

Case 15.—This case, which will be reported in detail elsewhere, is that of a 25-year-old male who sustained a perforating wound of the abdomen on May 14, 1945. A 25-caliber bullet entered the abdomen three inches below the ensiform cartilage, just to the right of the midline and passed out through the back at the level of the second lumbar vertebra. He was immediately paralyzed below the waist. A celiotomy, performed on the day of injury, revealed a large retroperitoneal hematoma. Ten days later, laminectomy was performed for the cord injury. Six weeks after the original injury, the patient complained of epigastric pain and, on examination, evidence of an arteriovenous fistula was observed.

Operation.—September 27, 1945. Under endotracheal nitrous oxide-ether-oxygen anesthesia, a left paramedian incision was made. Abdominal exploration revealed a large pulsating mass in the right upper quadrant. In order to expose the aorta, dissection was carried out in the extraperitoneal region, reflecting the contents of the left side of the abdomen to the right. The aorta was encircled by pieces of rubber tubing above and below the fistula which was present just below the right renal artery. The aorta was then dissected free from the aneurysm and the opening into the latter closed, with a running stitch. The opening into the aorta was closed with a transverse running stitch. After operation, although there was a stormy period for 12 days, due to urinary suppression and hypertension, the patient

made an excellent recovery. The peripheral pulses were normal. Figure 18 shows the patient five months after operation.

Case 16.—This 26-year-old male was wounded by shell fragments in the left thigh on March 30, 1945. He developed some numbness and tingling in his left foot and a pulsating mass 8 cm. below the inguinal ligament, directly beneath the scar of the wound. There was a systolic thrill and a high-pitched bruit over this mass but there was no diastolic component to the murmur. Arteriogram, August 10, (Fig. 19), revealed an aneurysm the size of a plum, arising from the upper portion of the superficial femoral artery. Lumbar sympathectomy was performed on October 4, 1945.

Operation.—October 18, 1945. The superficial femoral artery was exposed above the aneurysm, medial to the sartorius muscle. It was encircled by a piece of rubber tubing. Compression on this tubing now caused the aneurysmal sac to collapse. The artery below the aneurysm was then exposed, and a tube placed about it to control the retrograde circulation. With both the proximal and distal arteries occluded, the sac was exposed and incised. After removal of the clots and fresh blood, the openings of the afferent and efferent arteries were observed to be separated by approximately 1 cm. The artery was then freed from the sac by sharp dissection. There was considerable scar tissue, as well as some edema present. With the aid of traction applied by means of the rubber tubes, the orifices of the artery could be approximated. Accordingly, after cutting away excess portions of the sac, the opening was closed in a transverse fashion with a continuous running stitch. In addition, numerous interrupted stitches of silk were used in order to approximate the scar tissue wall of the sac so as to take tension off of the suture line. Upon release of the constricting tubing pulsatile flow took place across the suture line. The artery in this location appeared to be quite small and contracted. There was considerable distortion of the femoral artery at the site of suture. The wound was closed without drainage. The postoperative course was uneventful. Oscillations at the left ankle were about two-thirds normal. Arteriogram (Fig. 20), taken six weeks after operation, revealed considerable distortion of the femoral artery. Three months after operation, the patient reported recurrence of the bruit. Since there was considerable degeneration and fibrosis of the arterial wall in the region of the aneurysm, it is quite possible that this scar tissue had given way leading to recurrence.

FIG. 18. — Case 15: Five months after repair of abdominal aorta for arteriovenous fistula.

Case 17.—This 29-year-old male was wounded in the left thigh by mortar fragments on November 11, 1944. He sustained a compound fracture of the left femur. Six weeks after injury, an arteriovenous fistula was discovered close to the site of fracture. He was admitted to this Vascular Center on May 8, 1945. Arteriography (Fig. 21), on May 25, 1945, disclosed a simple arteriovenous fistula just below the fracture line. There was considerable distortion of the superficial femoral vein, probably due to the scar tissue about the fracture. Lumbar sympathectomy was performed on September 13, 1945. Collateral circulation was satisfactory following this procedure.

Operation.—October 18, 1945. Under continuous spinal anesthesia, an incision was made over the femoral vessels, and the sartorius muscle was retracted medially. The superficial femoral artery was exposed above the fistula and a piece of rubber tubing placed about the artery. Compression of the artery, at this point, obliterated the bruit of the fistula. The artery was then exposed below the fistula, carefully preserving the small branches, and was again controlled by rubber tubing in this location. The vessels at the site of the fistula were bound down in scar tissue. The communication was exposed by sharp dissection. With digital compression of the femoral vein above and below the fistula, the artery was cut

away from the vein. The vein was irrigated with saline and closed in a longitudinal fashion. The defect, in the artery measured 1 cm. in length, and the edges were composed of dense scar tissue. The intima of the artery was not rough. The damaged portion was excised in an elliptical fashion and the opening was closed in a transverse direction with a continuous running stitch. There was no bleeding from the suture line after release of the occluding tubes. The suture line occupied approximately three-quarters of the circumference of the vessel and caused considerable distortion at this point. However, good expansile pulsation was transmitted across the suture line. The wound was closed without drainage. After healing had taken place, oscillometry showed that there was greater pulsation on the affected side than on the normal side. Arteriogram (Fig. 22) after recovery, showed some distortion of the superficial femoral artery but preservation of the lumen. Three months after operation, the patient reported that there had been no recurrence of the aneurysm. His exercise was still limited, due to the stiffness of his knee resulting from the prolonged period of traction, and the leg tired more readily than normal.

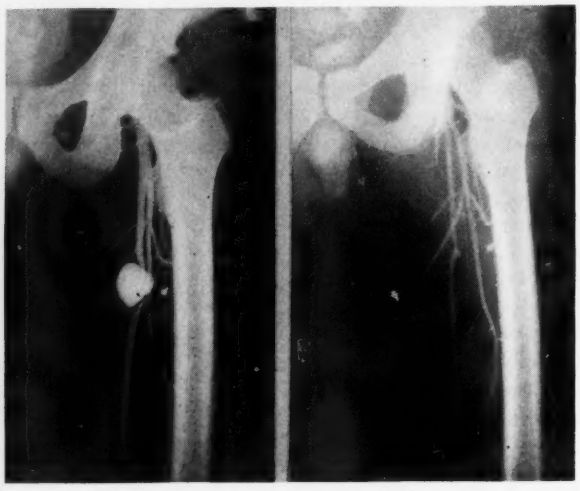


FIG. 19 FIG. 20

FIG. 19.—Aneurysm of superficial femoral artery. Case 16. Preoperative arteriogram.

FIG. 20.—Postoperative arteriogram. Case 16. After repair of superficial femoral artery.

Case 18.—This 23-year-old male was struck by fragments from a defective mortar shell on September 24, 1945. He sustained multiple wounds of the neck, left shoulder and arm. One fragment penetrated the left arm just above the elbow and lodged beneath the skin on the medial side of the arm. Débridement of the wounds was performed and he was transferred to a Regional Hospital. While there, a pulsatile swelling in the region of the brachial artery above the elbow was noted. This increased in size. Immediately after injury he had developed a wrist drop and some weakness of the left hand. With increase in the size of the hematoma, progressive paralysis of the median nerve developed. He was admitted to this Vascular Center on October 17, 1945. No oscillations were detectible at the left wrist. Because of the increasing size of the pulsating hematoma with compression of the median nerve, he was operated upon three days after admission to this hospital.

Operation.—October 20, 1945: A longitudinal incision was made over the medial side of the arm above the elbow, curving slightly outward at the lower angle of the wound. Upon opening the deep fascia, some discoloration of the fat was noted. A pneumatic tourni-

quet applied about the arm was inflated and the hematoma was incised, revealing some fresh blood and old clots. The median nerve was exposed and dissected free from the aneurysm. It was found to have been flattened out as it was stretched over this tumor. Rubber tubes were passed about the brachial artery above and below the laceration in the wall, and the artery was cut from the aneurysm. The tourniquet was then released but no further bleeding occurred. The damaged portion of the arterial wall was then excised leaving only approximately one-sixth of the circumference intact. By approximating the two sections of the artery, the defect in the wall was closed in a transverse direction using a continuous stitch of No. 000000 silk through all layers of the arterial wall. There seemed to be considerable spasm of the proximal artery but at the conclusion of the operation, a good pulsatile flow could be demonstrated distal to the suture line. The cavity of the aneurysm was drained through the wound of entrance on the lateral side of the arm and the incision was closed. Immediately after operation, the color of the hand was good and a faint radial pulse was palpable. By the next day, the radial pulse had returned to its full volume and oscillometry two weeks after operation showed that the pulsations at the wrist were greater on the affected side than on the normal side. Attempted arteriography was not successful in this case but, since it was possible to obliterate the left radial pulse by pressure localized to the brachial artery just above the elbow, it was felt that the arterial repair had probably been successful.

FIG. 21 FIG. 22

FIG. 21.—Preoperative arteriogram. Case 17. Healed compound fracture of femur, with arteriovenous fistula of femoral vessels.

FIG. 22.—Postoperative arteriogram. Case 17. After repair of superficial femoral artery.

Case 19.—This 30-year-old male sustained a penetrating shelf fragment wound of the left popliteal region on June 18, 1944. In February, 1945, he noticed a thrill in the popliteal space. He was admitted to this Vascular Center on April 3, 1945. At that times there was evidence of an arteriovenous fistula involving the vessels in the upper portion of the popliteal space. Attempted arteriogram, April 20, 1945, was unsuccessful. Lumbar sympathectomy was performed on August 10, 1945. There was a considerable increase in the oscillometry at the left ankle following this procedure.

Operation.—October 25, 1945: Under continuous spinal anesthesia, a curved incision was made across the popliteal space. The incision was deepened along the lateral border of the semimembranosus muscle in order to expose the popliteal artery. Exposure was very difficult due to the depth of the space. The fistula proved to be at a higher level than had been anticipated. The popliteal artery was, therefore, encircled by a rubber tube below the fistula and a pneumatic tourniquet was inflated about the thigh. The artery was then dissected from the vein. Considerable retrograde bleeding took place, which was controlled with difficulty. The opening in the popliteal vein was then closed with interrupted stitches. The artery was freed-up since it was adherent to the vein and to the aneurysmal sac. Following completion of this procedure, an attempt was made to suture the opening into the artery. This was performed with interrupted stitches of No. 000 silk, the sutures being inserted both in a transverse and in a longitudinal direction in order to control residual

bleeding. At the conclusion of this procedure the pulse was not well transmitted across the suture line. The wound was closed without drainage. Following operation, although there was adequate circulation to maintain the nutrition of the tissues, the ankle pulses were not present and oscillometry, two weeks after operation, revealed a marked reduction in the pulsations at the left ankle. Although the patient was able to walk, he developed intermittent claudication after a short distance.

Case 20.—This 35-year-old male was wounded December 3, 1944, by shell fragments in both thighs. After débridement and subsequent secondary suture, the patient developed a secondary hemorrhage from a wound in the right popliteal space. Examination at that time revealed the presence of a thrill and bruit characteristic of an arteriovenous aneurysm in this region. He was admitted to this Vascular Center on March 7, 1945. Arteriography, March 23, 1945, revealed an arteriovenous fistula in the popliteal space and, in addition, there was an aneurysm on the lateral side of the popliteal artery. Because of persistent poor collateral circulation, a right lumbar sympathectomy was performed on September 13, 1945. After sympathectomy it was thought that the sac of the popliteal aneurysm became even larger than before operation.

Operation.—October 25, 1945: With the patient under continuous caudal anesthesia, the artery was exposed in the popliteal space above the aneurysm. It was enormously dilated. Below the fistula the artery was again considerably dilated. With compression of the popliteal artery above and below the fistula by rubber tubing, the bruit was completely abolished. Accordingly, the pneumatic tourniquet which had previously been placed about the upper part of the thigh, was inflated and the artery was cut away from the vein. There was considerable back bleeding from the venous side, which was controlled by digital pressure until the opening into the vein could be sutured. In addition to the fistula between the popliteal artery and vein, a small aneurysm, 1 cm. in diameter, was found on the medial side of the popliteal artery. After irrigation of the lumen of the artery with normal saline solution, it was found that, although the artery was considerably dilated both above and below the fistula, the wall seemed to be composed of good tissue and the intima was smooth. The two defects in the arterial wall were closed separately with No. 000 silk. After release of the pneumatic tourniquet, good expansile pulsation of the artery distal to the suture line was apparent. The incision was closed without drainage. Immediately after operation, the posterial tibial pulse was palpable and the color of the foot was excellent. Oscillometry after recovery from operation was almost normal. An arteriogram (Fig. 23) showed that the continuity of the artery had been preserved. However, there was considerable dilitation both proximal and distal to the point of repair. A phlebogram taken on the same day showed that the popliteal vein had been occluded. Three months after operation, he reported that there had been no recurrence of the aneurysm, but that he had some swelling of the foot and lower leg with dependency. He also developed some cramps in his upper calf on climbing hills.

Case 21.—This 21-year-old male was wounded on May 8, 1945. A 25-caliber bullet passed through the midportion of both thighs. He developed drop foot and anesthesia of the left foot, probably on an ischemic basis. Sometime after injury, during the process of evacuation, he noted a thrill in the left thigh. Upon admission to this Vascular Center, June 20, 1945, there were characteristic signs of an arteriovenous fistula involving the midportion of the left superficial femoral vessels. Arteriography, July 20, 1945, confirmed the diagnosis. Oscillometry showed a considerable reduction in the amplitude of pulsations at the left ankle but because of adequate collateral circulation and the possibility of arterial repair, sympathectomy was not performed. Satisfactory recovery from the nerve lesion was apparent.

Operation.—October 29, 1945: Under continuous spinal anesthesia, the superficial femoral artery was exposed in the midthigh and was occluded by rubber tubing passed above and below the fistula. The artery was then dissected free from the vein and the bleeding controlled by digital pressure until the vein could be sutured in a longitudinal fashion.

The damaged portion of the arterial wall was then excised and the defect was closed in a transverse direction. Good expansile flow took place after release of the rubber tubing. The wound was closed without drainage. Postoperatively, there were no complications and the pulses at the ankle were excellent. Oscillometry revealed equal pulsation of the arteries at both ankles. Arteriography three weeks after operation demonstrated the patency of the artery and phlebography showed that the vein was not obstructed. Three months later, he reported that the leg became weak after any extensive exercise, but that there had been no recurrence of the aneurysm. Since he also had partial paralysis of the sciatic nerve with moderate flexion deformity of the left knee, the residual symptoms may be more on a neurologic than a vascular basis.

FIG. 23. — Postoperative arteriogram. Case 20. There is considerable dilatation of the femoral artery above and the popliteal artery below the site of the former arteriovenous fistula.

Case 22.—This 33-year-old male was struck by a shell fragment in the right thigh, March 18, 1945, and sustained a laceration of the popliteal nerve. He was operated upon in a Forward Area, April 21, 1945, and a neurorrhaphy performed. At this time an arteriovenous fistula of the right popliteal artery and vein was discovered. At the time of admission to this Vascular Center, July 4, 1945, he already showed evidence of recovery in nerve function. There were classical signs of an arteriovenous fistula involving the vessels of the popliteal space. Attempts to visualize the aneurysm by arteriography were unsuccessful. A lumbar sympathectomy was performed on July 30, 1945. Following this operation there was improvement in the collateral circulation.

Operation.—November 5, 1945.—Under continuous caudal anesthesia, the popliteal artery was exposed in the upper portion of the popliteal space by a longitudinal incision just lateral to the tendon of the semimembranosus muscle. The artery was greatly dilated. It was controlled by a piece of rubber tubing attached to a Bethune tourniquet. Compression of the artery at this point now obliterated the thrill in the aneurysm although the bruit still persisted. Incision was then made on the lateral side of the popliteal space extending from behind the head of the fibula upward medial to the biceps tendon. The common peroneal nerve was exposed and followed to its junction with the posterior tibial. Tantalum foil, which encased the posterial tibial nerve for a distance of 2.5 inches, was removed. The peroneal nerve was retracted laterally and the posterior tibial medially to expose a greatly dilated popliteal vein. Numerous branches were divided and ligated and the vein was retracted medially to expose the popliteal artery below the fistula. This artery was now compressed by a piece of rubber tubing. The popliteal vein was controlled by sections of rubber tubing, above and below the fistula. With all four vessels now compressed, there was still audible a faint continuous bruit, with excessive pressure within the popliteal vein. Further dissection disclosed a small aneurysmal sac, approximately 2 cm. in diameter. From the apex of this sac the inferior lateral geniculate artery was derived. After controlling the retrograde circulation through this vessel, the popliteal artery was dissected free from the vein. The opening into the vein measured approximately 1.5 cm. in length and was closed in a transverse direction by a running stitch of No. 000 silk. The popliteal artery was badly scarred and bound down in the region of the aneurysm. It was dissected free from the sac. There were two defects in the arterial wall, one which measured 1 cm. in diameter where the communication with the vein had been located, and a second larger defect at the site of the aneurysm. The damaged portion of the arterial wall was cut away transforming the two holes into one large defect, which occupied three-fifths of the circumference of the vessel.

The intima and media of the popliteal artery appeared normal and, accordingly, a transverse suture was performed using No. 000 black silk. Thirty minutes after completion of the procedure, excellent pulsation was present below the suture line. The wound was closed without drainage. Convalescence was uneventful and oscillations at the two ankles were equal. Arteriography was not successful. Three months after operation, the patient reported that there had been no recurrence of the arteriovenous fistula and that there was satisfactory progress in the regeneration of the nerve. He was still troubled with swelling above the ankle, but the circulation to the leg appeared excellent.

COMMENT.—Of the 17 cases in which transverse repair of the artery was attempted, it was successful in 15. Restoration of the continuity of the artery was demonstrable by arteriogram in ten of these cases and in the other five by the persistence of normal pulses distal to the site of repair. Of the two unsuccessful attempts, thrombosis occurred at the suture line in one patient (Case 19), but this was in part due to faulty technic in not obtaining adequate control of the artery above the fistula. In the second individual (Case 16), repair was attempted of an arterial aneurysm. Scar tissue of the aneurysmal wall was used to reinforce the suture line. The patient has reported recurrence of his aneurysm. It may well be that this scar tissue has given way, permitting this new aneurysm to form.

DISCUSSION.—The value of arterial repair in the treatment of aneurysms and arteriovenous fistulae may be questioned. Since the incidence of gangrene after ligation of major arteries of the extremities in the treatment of these lesions is negligible, the question may rightly be raised: "Why subject the patient to the risk of repair?" While it is true that gangrene is rare after excision of these injured arteries the end-results are often not favorable. Bigger[2] has written: "In the literature dealing with the treatment of traumatic vascular lesions of important blood vessels, much is said, and properly, about the cure of the lesion and the avoidance of acute ischemia and gangrene, but remarkably little consideration is given to the permanent reduction of blood supply to the tissues, especially the muscles, distal to the lesion." While it is true that after excision the development of collateral circulation will usually suffice to care for the metabolic requirements of the tissues at rest, it is only rarely that some impairment of circulation is not noted.

In reply to a questionnaire sent to the patients from this Vascular Center in whom either the popliteal or the femoral artery had been ligated for an arteriovenous fistula during the past year, nine out of 12 individuals complained of restriction in their activities. Intermittent claudication came on after walking from two to five blocks. In comparison, of 11 patients in the present series after repair of popliteal or femoral arteries for arteriovenous aneurysms, only two complained of intermittent claudication and symptoms came on in these patients only after walking six to eight blocks.

Oscillometric readings before operation in 12 patients were on the average 2.77 units on the affected side and 4.44 on the opposite normal side. After arterial repair the average oscillations of these same patients were 3.85 on the affected side and 3.79 on the normal side. By comparison, in ten patients

in whom the major artery was ligated the average oscillometric readings before operation were 2.72 on the affected with 5.0 on the normal side. After operation the values were 0.75 and 4.0, respectively. Arterial repair, therefore, increased the oscillometric readings from an expected 0.75 to an average of 3.85 units. It is well known that the circulation may be quite adequate for tissue nutrition even in the absence of arterial oscillations but the preservation of pulsatile arterial flow through the major arteries is naturally to be preferred.

Even granted that preservation of the continuity of the artery is to be preferred the question may still be brought up of the possible risk to the patient. The dangers of hemorrhage or infection do not appear to be increased by arterial repair. In only one patient (Case 4) was serious infection encountered. Hemorrhage did not occur in any case in this series. The major objection to arterial repair in the past has been the recurrence of the fistula or the development of a false aneurysm close to the site of repair. In three of the five cases reported by Pemberton and Black,[7] ligation of the communication or restorative endaneurysmorrhaphy was followed by recurrence of the fistula. One patient in our series (Case 3) developed recurrence after transvenous suture. Of more significance is the possibility of the development of a false arterial aneurysm after closure of the fistula. Direct measurements of pressures within arteriovenous fistulae[18] in 11 patients have shown an average mean pressure of only 40 mm. of mercury. By comparison, in 12 patients with arterial aneurysms, the average mean pressure was 84 mm. of mercury. According to these figures then, closure of the communication between the artery and vein should approximately double the mean pressure. It is quite to be expected that any weak point in the arterial wall would give way with this increase in pressure.

The incidence of additional points of damage of the arterial wall in the presence of arteriovenous fistulae is high. Two defects, one communicating with the main vein and the other with an aneurysmal cavity or another vein, were found in six cases in this series and three venous communications were present in one patient (Case 3). Reid and McGuire[8] have reported one case in which a second communication was overlooked at the original operation and Holman[9] has observed a second case. Only by completely isolating the artery from the surrounding tissues can the presence of additional communications or damaged areas of the arterial wall be discovered. Generalized dilation of the artery to form a fusiform aneurysm following closure of an arteriovenous fistula has been described by Reid,[6] and by Bigger.[2] In each of their cases the fistula was of long duration with marked degenerative changes in the arterial wall. The average duration of the fistula in the patients reported in this series was only eight months and the longest-standing case was 14 months. Dilatation of the artery, especially proximal to the fistula, was frequently observed (Case 21) but rarely was there calcification. No attempt at repair was made in the presence of degenerative changes.

After careful inspection of the arterial wall the damaged portion was generally removed. In 11 cases in the present group a portion of the arterial

wall was excised. Particular emphasis was placed on this procedure since it is believed that only the presence of normal arterial wall composed of muscular and elastic tissue can prevent subsequent dilatation. Although the use of the wall of the sac or a segment of vein to reconstruct the arterial wall has been advocated by Matas[19] it does not seem likely that this material which is largely composed of fibrous tissue can withstand the increased pressure. Makins[1] has condemned the use of such flaps in the repair of arterial defects. The fact that such tissue is not an effective limiting barrier is shown by the tendency of aneurysms to expand. To use scar tissue to buttress the line of suture affords only a false sense of security. The recurrence of the arterial aneurysm in Case 16 is illustrative of the futility of using anything but normal arterial wall in the repair.

After excision of part of the arterial wall the resultant defect must be closed by approximation of the edges of the incision. Learmouth[17] has stated that an artery cannot be stretched. In the presence of an arteriovenous fistula, however, the artery, especially the proximal portion, has generally become so dilated that sufficient length is already available. Approximation is readily obtained by means of the rubber tubing which is used to occlude the artery above and below the fistula (See Fig. 10).

It has generally been found desirable to use any sound portion of the arterial wall, even to one-sixth of the circumference (Case 18), rather than to perform a complete transsection with end-to-end anastomosis. Mobilization of the artery may be impossible due to important branches. According to Learmouth[17] "the length over which vessels can be freed and mobilized is governed by the points of origin of branches which are indispensable for the collateral supply, if the repair is not successful." In no case was a significant collateral artery sacrificed in order to attempt repair of the major vessel.

Holman[18] has emphasized the fact that arterial repair in the presence of arteriovenous fistula depends upon the "ability to control completely all bleeding, either by the tourniquet proximal to the lesion, or by numerous well-placed bulldog arterial clamps, as described by Matas." Linton[20] has advocated the use of the Bethune tourniquet in order to control the deeper-seated major blood vessels. The use of rubber tubing has been most satisfactory in our cases and, when split, it may be fitted to a Bethune tourniquet with equally good results. After surrounding the vessel with the section of rubber tubing (cf. Fig. 10) it has been clamped close to the arterial wall with fine curved mosquito hemostats. No damage to the arterial wall has been observed and approximation of the edges of the incised vessel has been facilitated.

Complete control of the arterial supply to an arteriovenous fistula is essential for repair. Failure in the one case in which this was not achieved (Case 19) serves to emphasize the importance of this procedure. The use of a sterile stethescope at the time of operation has been found to be invaluable in confirming the completeness of the control of the arterial component. Occlusion of the principal afferent and efferent arteries alone may not suffice. Persis-

tence of a continuous bruit signifies that some additional arterial supply is present. As long as there is arterial blood passing through the fistula, to sever the connection is hazardous.

Complete control of the venous component facilitates the repair but may require prolonged and tedious dissection and may result in destruction of collateral vessels. In eight patients both arteries and veins were secured proximal and distal to the fistula by segments of tubing and heavy thread. In seven patients, however, control of the arteries alone was achieved. At the moment of severing the connection between the artery and the vein or aneurysmal sac, digital pressure was used to control the venous bleeding. Suture of the open vein was then readily accomplished. In five other cases, after the afferent and efferent arteries had been isolated a pneumatic tourniquet, which had previously been placed at a higher level about the extremity, was inflated. This procedure was not especially useful since the venous system in the presence of an arteriovenous fistula was capacious and already full of blood. Retrograde bleeding generally necessitated digital pressure in addition to the proximal tourniquet. Frequently the venous pressure appeared to be even higher than without the tourniquet.

Once the artery has been disconnected the opening into the vein can be closed longitudinally with a running stitch. This procedure was employed mainly for the purpose of simplicity in dealing with the venous component of the fistula since it is rarely necessary to repair the vein. The continuity of the left innominate vein in Case 4 was preserved especially since the thoracic duct emptied into it. Phlebography after suture of the vein in 12 cases showed the vein to be patent in six and obstructed in the other six patients. In an additional five cases in which the vein was sutured, even though arterial repair could not be performed, patency was demonstrable in three and thrombosis in two. No instance of thrombophlebitis or pulmonary embolism was encountered. These complications would, therefore, appear to be no more of a hazard from suture of the vein than from its ligation since cases of embolism have been reported by Reid,[6] and by Linton and White[21] after ligation.

Arteriography has been helpful in the study of patients with arteriovenous fistulae. Before operation it has served in the accurate localization of the lesion and in demonstrating the location of important collateral vessels. Again, it has helped to show the presence of an aneurysmal sac (Case 5). In the presence of such a sac considerable destruction of arterial wall can be anticipated with consequent reduction in the chances of successful repair. Following operation arteriograms have been useful in disclosing the true state of continuity of the artery (Case 5). In addition they may show early evidence of general dilatation (Case 20) or satisfactory progress of the local lesion (Case 10).

The rôle of sympathectomy in the repair of arterial lesions is not clear. Thirteen of the patients in this series were treated by prophylactic sympathectomy before operation on the arterial lesion. Of this number two attempted

repairs failed. Sympathectomy was not performed in ten patients. Arterial thrombosis occurred in only one of these cases. It is possible that sympathectomy might have prevented arterial spasm though Homans[22] has reported that sympathetic procaine block has not been successful in relieving traumatic arterial spasm. It is probable that a swift flow of blood prevents thrombosis at the suture line. Possibly sympathectomy may have promoted increased volume flow of blood and in this way have improved the chances of successful repair.

Transverse closure of the defect in the arterial wall may produce distortion and turbulence of the blood stream. In fact, auscultation over the vessel at the suture line reveals a loud sharp systolic murmur and this sound is even audible through the skin and soft tissues after healing has taken place. Without a diastolic component it has no significance. Although distortion is produced by the transverse closure it is likely that the greater diameter at this point prevents thrombosis and in this way increases the likelihood of successful repair.

SUMMARY

Arterial repair was attempted in the treatment of 23 aneurysms and arteriovenous fistulae. Success was demonstrable either by arteriography or by the presence of normal peripheral arterial pulsations in 18 of these attempts. In one case, recurrence of an arterial aneurysm was subsequently reported by the patient. In a second patient, recurrence of an arteriovenous fistula followed transvenous suture. Subsequent excision of the lesion was necessary. Thrombosis at the suture line occurred in three patients but the collateral circulation proved sufficient to prevent gangrene. Repair of the defect in the wall of the vein was performed on 18 occasions. Phlebography in 12 of these cases after recovery demonstrated the patency of the vein in six patients but in six others postoperative studies showed the vein to be occluded. No instance of thrombophlebitis or pulmonary embolism was encountered. Transverse suture of the defect in the arterial wall after excision of the damaged portion has been found more satisfactory than longitudinal suture, end-to-end anastomosis or transvenous repair. Oscillometry, after arterial repair, has demonstrated marked improvement in pulsatile circulation in patients after repair of arterial lesions in comparison to a control group who were treated by quadruple ligation and excision of the arteriovenous fistula.

The functional capacity, especially as shown by freedom from intermittent claudication, is increased in patients when the continuity of the major artery to the extremity is preserved.

The arteriograms appearing in this article are reproduced by permission of the Museum and Medical Arts Service, U. S. Army Medical Museum.

REFERENCES

1 Makins, G. H.: Gunshot Injuries to the Blood Vessels. John Wright and Sons Ltd., Bristol, 1919, p. 87.

2 Bigger, I. A.: Treatment of Traumatic Aneurysms and Arteriovenous Fistulae. Arch. Surg., **49**, 170, 1944.
3 Matas, R.: An Operation for the Radical Cure of Aneurysm Based upon Arteriorrhaphy. ANNALS OF SURGERY, **37**, 161, 1903.
4 Bickham, W. S.: Arteriovenous Aneurysms. ANNALS OF SURGERY, **39**, 767, 1904.
5 Reid, M. R.: Abnormal Arteriovenous Communication. IV. The Treatment of Abnormal Arteriovenous Communications Acquired and Congenital. Arch. Surg., **11**, 237, 1925.
6 Reid, M. R.: Studies on Abnormal Arteriovenous Communications Acquired and Congenital. I. Report of a Series of Cases. Arch. Surg., **10**, 601, 1925.
7 Pemberton, J. de J., and Black, B. M.: Surgical Treatment of Acquired Aneurysm and Arteriovenous Fistula of Peripheral Vessels. Surg. Gynec. and Obst., **77**, 462, 1943.
8 Reid, M. R., and McGuire, J.: Arteriovenous Aneurysms. ANNALS OF SURGERY, **108**, 643, 1938.
9 Holman, E.: Personal communication.
10 Matas, R.: Arteriovenous Fistula of Femoral Vessels. S. Cl. North Am., **2**, 1165, 1922.
11 Holman, E.: Arteriovenous Aneurysms. The MacMillan Co., New York, 1937.
12 Postempski: Arch. ed atti d. soc ital. di chir., Roma, **2**, 58–61, 1886.
13 Matas, R.: Keen's Surgery. W. B. Saunders Co., Phila., 1908, Vol. 5, p. 216.
14 Waugh, W. G.: Arteriovenous Aneurysm of the Popliteal Vessels: Arteriorrhaphy under Heparin. Brit. J. Surg., **31**, 192, 1943.
15 Murphy, J. B.: Resection of Arteries and Veins Injured in Continuity—End-to-end Suture—Experimental and Clinical Research. Medical Record, **51**, 73, 1897.
16 Carrell, A.: The Surgery of Blood Vessels. J. Hopkins Hosp. Bul., **18**, 18, 1907.
17 Learmouth, J. R.: The Surgery of Blood Vessels. Edin. Med. Jour., **47**, 225, 1940.
18 Freeman, N. E.: Direct Measurement of Blood Pressure within Arterial Aneurysms and Anteriovenous Fistulae. Surgery—To be published.
19 Matas, R.: Some Experiences and Observations in the Treatment of Arteriovenous Aneurysms by the Intrasaccular Method of Suture (Endo-aneurysmorrhaphy): With Special Reference to the Transvenous Route. ANNALS OF SURGERY, **71**, 403, 1920.
20 Linton, R. R.: Arterial Embolism. Surg. Gynec. and Obst., **80**, 509, 1945.
21 Linton, R. R., and White, P. D.: Arteriovenous Fistula between the Right Common Iliac Artery and the Inferior Vena Cava. Arch. Surg., **50**, 6, 1945.
22 Homans, J.: Vascular Disorders of the Extremities. New Eng. J. Med., **226**, 917, 1942.

DISCUSSION.—DR. RUDOLPH MATAS, New Orleans, La.: It appears to me that the tendency of operators in this war has been to disregard the conservative treatment of the arteriovenous aneurysms. This is due chiefly to a general belief that the collateral circulation in the arteriovenous aneurysms is so well-developed when the operation is delayed, that conservative methods directed toward the saving of the artery are superfluous. While I agree that in many and, perhaps, the majority of the "mature" (long-standing) A-V aneurysms the fistulous tract and attached vessels may be safely excised or ligated, this is not true of many cases in which the sacrifice of the artery may be followed by disastrous consequences — this being particularly true of the carotid and popliteal and common femoral fistulae, especially when the operations are performed too soon after the fistula has been established.

Fistulous communications between an artery and contiguous vein caused by punctures, stabs or the penetration of small projectiles of high velocity; and sharp metallic splinters of exploding shells and bombs in which the artery is not damaged, dilated or deformed, are particularly favorable for repair and cure by the method of *transvenous suture* in which the fistula is exposed, and closed by suturing the orifice from the venous side, with conservation of the artery and sacrifice of the vein.

When the artery is damaged in any way, the problem of repair becomes more difficult, and other devices besides the transvenous and the intrasaccular suture must be sought. In the great majority, the tests for an adequate collateral circulation will show that by prolonging the delay in operating, surgical interference may become safe by an ultimate development of the collaterals. When complications arise, such as cardiac failure from the fistula, that call for its quick closure, and the circulation is inadequate, the excision of the fistulous tract with a circular anastomosis of the artery, is in order, to maintain the arterial circulation. This is a procedure that is, indeed, seldom required. I have never had to resort to it in my large experience. Doctor Elkin, likewise, states that he has never had to apply a secondary arteriorrhaphy for an excised A-V aneurysm. The German surgeons did resort to it quite often in World War I. There can be no doubt that in modern warfare, the indications for an immediate anastomosis for divided or obliterated arteries as the popliteal, femoral and carotids, do occur quite often, but the conditions for reparative and reconstructive operations on the blood vessels are too rare and difficult on the battlefield.

In civilian practice, where there is less haste, the opportunities for reparative surgery of the arteries and arteriovenous aneurysms are more frequent, but are seldom utilized by men who have been trained to perform radical excisions or quadruple ligatures in A-V fistulae.

Doctor Freeman, always striving at conservatism and repair, has gone further than I, in my civilian practice, with A-V aneurysms. For, in suitable cases he detaches the inosculating vessels, closes the lateral wound in the vein, and then divides the artery through the fistulous tract with a segment of the damaged artery. Finally, he restores the arterial circulation by doing an end-to-end anastomosis. Doctor Freeman has certainly had a very remarkable experience. The fact that in 24 cases in which a circular arteriorrhaphy was performed, 20 were successful in maintaining the arterial circulation, speaks eloquently for a high degree of technical skill with the needle which is rare among otherwise skillful surgeons. Doctor Freeman is entitled to praise and congratulations not only for his technical skill but for his brilliant demonstration of the efficiency of repair and conservatism in arteriovenous surgery.

With the kind permission of the Chair, I will now avail myself of a brief interval to exhibit lantern slides taken from patients in my own practice, in which transvenous suture methods originally devised by Bickham and myself, 43 years ago, for the cure of arteriovenous aneurysms will be exhibited in their application to A-V aneurysms of the innominate, subclavian, carotid, external iliac, femoral and popliteal.

Dr. Isaac A. Bigger, Richmond, Va.: One patient with femoral fistula developed evidence of vascular insufficiency, even though the distal arterial segment pulsated strongly following resection of the fistulous area. This suggests that there may be regression of the collateral bed after removal of a fistula.

Dr. Norman E. Freeman, Auburn, Calif. (closing): I wish to thank Doctor Matas and Doctor Bigger for their valuable comments. In regard to the transvenous closure of a false communication between an artery and vein, I should like to re-emphasize the danger of overlooking some additional opening or weak point in the arterial wall. With the rise in arterial pressure which occurs as soon as the fistula is closed, there is a real possibility that an additional, and possibly unsuspected, defect in the muscular and elastic coats of the arterial wall will give way, leading to the development of an arterial aneurysm.

As to the possibility of regression in the collateral bed after removal of a fistula, that would hardly seem likely in the presence of impaired circulation. Although the exact mechanism is obscure there is evidence that the stimulus for the development of collateral circulation is closely related to the need for blood flow. And even when

a superabundant circulation is produced by closure of an arteriovenous fistula, the extracollateral channels do not disappear. We have studied by means of arteriography the distribution of arterial pathways following spontaneous closure of arteriovenous fistulae in four patients. Even though the circulation through the main artery is restored by this spontaneous closure, one can still observe the dilated and tortuous collateral vessels filled with radioopaque dye. Oscillometric readings, following restoration of the continuity of the main vessel, will frequently be greater immediately after operation than some weeks later. This observation would suggest that some contraction of the vascular bed occurred but not in the presence of superabundant flow. The presence of symptoms of arterial insufficiency after excision of an arteriovenous fistula, in spite of a positive Henle-Coenen sign, *i.e.*, pulsation of the distal end of the artery, might be interpreted as further evidence for the concept which Doctor Bigger has advanced. Although the circulation is adequate when the part is at rest, the collateral vessels do not have sufficient capacity to expand to care for the metabolic demands created by exercise.

STATEMENT OF THE OWNERSHIP, MANAGEMENT, CIRCULATION, ETC., REQUIRED BY THE ACTS OF CONGRESS OF AUGUST 24, 1912, AND MARCH 3, 1933
Of ANNALS OF SURGERY, published monthly at Philadelphia, Pa., as of November 1, 1946.

State of Pennsylvania } *ss.*
County of Philadelphia }

Before me, a Notary Public in and for the State and county aforesaid, personally appeared Ellis W. Bacon, who, having been duly sworn according to law, deposes and says that he is the Treasurer of the ANNALS OF SURGERY and that the following is, to the best of his knowledge and belief, a true statement of the ownership, management (and if a daily paper, the circulation), etc., of the aforesaid publication for the date shown in the above caption, required by the Act of August 24, 1912, as amended by the Act of March 3, 1933, embodied in section 537, Postal Laws and Regulations, printed on the reverse of this form, to wit:

1. That the names and addresses of the publisher, editor, managing editor, and business managers are: Publisher, J. B. Lippincott Company, E. Washington Square, Philadelphia, Pa. Editor, Dr. Walter E. Lee, Chairman Editorial Board, 1833 Pine Street, Philadelphia, Pa. Managing Editor, Dr. James T. Pilcher, 121 Gates Avenue, Brooklyn, New York; Business Manager, O. T. Leeman, E. Washington Square, Philadelphia 5, Pa.

2. That the owner is: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding one per cent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a firm, company, or other unincorporated concern, its name and address, as well as those of each individual member, must be given.) J. B. Lippincott Company, E. Washington Square, Philadelphia, Pa.; Ellis W. Bacon, Wallingford, Pa.; Sarah L. Biddle, Bethayres, Pa.; Bertram Lippincott, Penllyn, Pa.; Joseph W. Lippincott, Bertram Lippincott and the Pennsylvania Company for Insurances on Lives and Granting Annuities, Trustees under Will of J. Bertram Lippincott, Philadelphia, Pa.; J. W. Lippincott, Bethayres, Pa.; Marianna L. O'Neill, Rydal, Pa.; Pennsylvania Company for Insurances on Lives and Granting Annuities, Trustee Estate of Craige Lippincott, Philadelphia, Pa.; Fidelity Philadelphia Trust Company, Trustee Estate of Walter Lippincott, Philadelphia, Pa.; Howard K. Bauernfeind, Chicago, Illinois; George Stevens, Kingston, N. J.

3. That the known bondholders, mortgagees, and other security holders owning or holding 1 per cent or more of total amount of bonds, mortgages, or other securities are: None.

4. That the two paragraphs next above, giving the names of the owners, stockholders, and security holders, if any, contain not only the list of stockholders and security holders as they appear upon the books of the company but also, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting, is given; also that the said two paragraphs contain statements embracing affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner; and this affiant has no reason to believe that any other person, association, or corporation has any interest direct or indirect in the said stock, bonds, or other securities than as so stated by him.

[Signed] ELLIS W. BACON.

Affirmed to and subscribed before me this 30th day of September, 1946.
[Seal] HARRY J. BEARD.

(My commission expires March 5, 1949.)

ROENTGENOLOGIC KYMOGRAPHIC STUDIES OF THE HEART IN THE PRESENCE OF AN ARTERIOVENOUS FISTULA AND THEIR INTERPRETATION*

EMILE HOLMAN, M.D.
SAN FRANCISCO, CALIFORNIA

THE EFFECTS of an arteriovenous fistula upon the heart and circulation have been the subject of numerous clinical observations,[1-5] much philosophical discussion,[6-14] and extensive experimentation.[15-20] Often the observed facts have seemed contradictory and their explanation has, therefore, been elusive. More often than not, observations have been recorded without attempts at explanation. But the mere recording of observed facts is not as important as determining their sequence and their *"raison d'etre."* Having determined a logical explanation for certain phenomena,[21] one should seek constantly to verify or disprove it. Such an opportunity was provided recently by two cases of arteriovenous fistula in which cardiac silhouettes were obtained by roentgenologic kymography. Very significant changes in the silhouette occurred, providing important information as to the sequence of events that occurs in the circulatory apparatus on closing or opening a fistula. Moreover, instructive evidence was obtained applicable to the explanation of the almost mysterious retardation in pulse rate that accompanies the closure of a large fistula.[22]

CASE REPORTS

CASE 1.—Fifteen years ago, J. P., age 52, was shot through the soft tissues of the left popliteal space. Two operations were performed within the following week, accompanied by a great loss of blood at each operation. Despite an infection, recovery occurred without other complications. His general health had been excellent until the two years preceding his admission to the hospital in September, 1945, when he had noted gradually increasing shortness of breath and weakness and swelling of his left leg (Fig. 1). A palpable thrill had been present along the course of the femoral vessels ever since the accident. Several ulcers had appeared on the inner aspect of the left ankle, the last one having healed about four years ago.

Physical examination revealed an enlargement of the heart over which one could hear a rough, blowing systolic murmur particularly in the pulmonic area.

The left leg was definitely larger than the right, with prominent varicosities of thigh and leg. The left femoral artery below the inguinal ligament was greatly dilated and remarkably tortuous down to the popliteal space. Along its course was a continuous palpable thrill and audible bruit, so intense in the midthigh that one was almost led to believe that the communication lay here rather than in the popliteal space; however, pressure in the latter area over the bullet track completely controlled the thrill and bruit proximal to it, thus eliminating the possibility of an abnormal communication other than that in the popliteal space. The intense thrill

*Read before the American Surgical Association, April 2-4, 1946, Hot Springs, Virginia.

in the thigh was ascribed to the eddies set up in the large proximal vein by blood flowing rapidly through the large popliteal fistula.

At operation, October 2, 1945, performed during the first half without a tourniquet,[23] the fistula was found to be a direct lateral communication between the popliteal artery and vein. The proximal artery was 2.5 cm. in diameter, whereas distal to the fistula the artery was only 0.7 cm. in diameter. The popliteal vein both proximal and distal to the fistula was 2.8 cm. in diameter.

FIG. 1. — Case 1: Photograph in presence of large left popliteal fistula showing large varicosities beyond the fistula, large dilated heart, and marked tortuous dilatation of artery proximal to fistula.

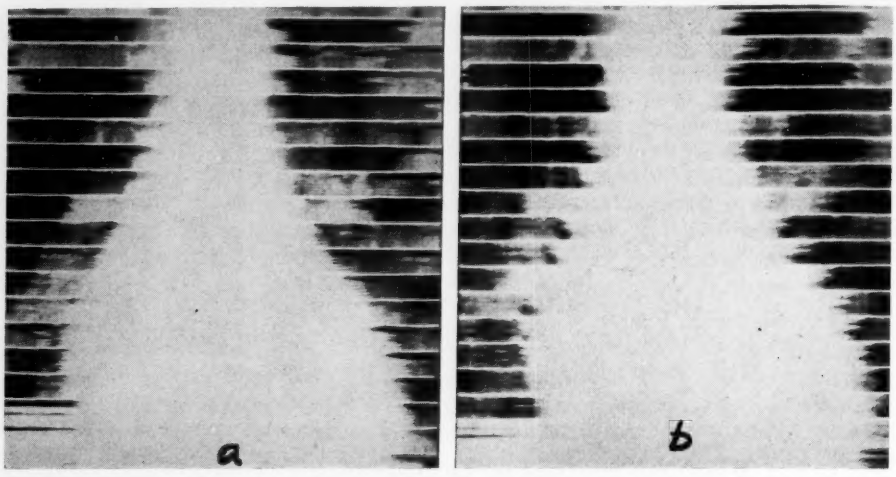
The Henle-Coenen[24, 25] phenomenon was absent: *i.e.*, when the artery proximal to the opening was closed, there was no pulsation either in the artery just distal to the opening, or in the posterior tibial artery at the ankle. Hence restoration of the artery was considered desirable in order to insure an adequate circulation in the leg beyond the fistula. When the Henle-Coenen phenomenon is present, *i.e.*, when the artery pulsates distal to the site of closure, we may assume that the arterial collateral circulation is adequate for the life of the limb, and the artery may be divided with impunity. Since pulsating vessels are more easily identified and mobilized than are collapsed vessels, the artery and vein both proximal and distal to the fistula were isolated in the distended state. Following the inflation of a pneumatic tourniquet on the upper thigh the vein was opened longitudinally just opposite the fistula, which in the collapsed state of the vessels was found to measure 1.5 cm. in diameter. As the collapsed artery was half its original size, one may infer that the fistula when transmitting blood was at least 2 to 2.5 cm. in diameter. The rent in the artery was closed with a running suture of doubled silk approximating the edges of the arterial opening, reinforced with several interrupted sutures of silk. The posterior leaf of the incised venous wall was sutured to lie over the line of the arterial closure, and the anterior leaf of the vein was imbricated over the posterior leaf. The vein proximal to the fistula was permanently ligated, whereas below the fistula the vein was both ligated and divided. Deflation of the thigh tourniquet was followed by vigorous pulsation in the posterior tibial and dorsalis pedis arteries.

The wound healed *per primam*. There was marked localized tenderness over the dilated tortuous artery of the thigh for several days, which gradually subsided without evidence of clotting.

CASE 2.—A 20-year-old army recruit was seen in brief consultation for a greatly swollen right thigh and lower leg incident to an arteriovenous fistula of the common femoral vessels following a gunshot wound three years previously. Despite the greatly swollen leg and a dilated heart, he had been inducted into the service, but since he refused an operation for the elimination of the fistula, he was discharged from the army. Before his discharge, kymographic studies were made revealing a marked widening of the aortic arch and additional dilatation of the already dilated heart on closing the fistula (Fig. 2). General blood pressure rose from 110/60 to 150/84 on closing the fistula accompanied by a drop in pulse rate from 76 to 48. This increase in pressure and resulting retardation in pulse indicated a considerable increase in total blood volume. It is interesting to record that his head felt "full" and his chest "tight," when the fistula was closed, suggesting a filling-up of the arterial vessels in these two areas when the fistula was temporarily eliminated from the circulatory bed.

The following special studies in Case 1 before and after operation were of more than usual interest:

Blood Pressure.—Compression of the artery anywhere in the thigh proximal to the popliteal area caused an elevation of pressure from 100/60 to 160/80 for several beats, subsiding promptly to 146/72 as long as the fistula was closed (Fig. 3). The rise in pressure was accompanied by a marked retardation in pulse from 75 to 48. Both pressure and pulse returned to normal on release of the compression. At



A B

FIG. 2.—Case 2: (A) Roentgenographic kymogram in which during first half of exposure a femoral fistula was closed, and during the second half it was open.
(B) Roentgenographic kymogram in which during first half of the exposure, the fistula was open and during second half of exposure it was closed. Note marked widening of aortic arch during closure of fistula and evidence of further distention of an already dilated left ventricle on closing the fistula.

operation, closure of the fistula by digital pressure caused a rise in blood pressure from 120/80 to 170/100, and a slowing of pulse from 80 to 48. Following operation, the blood pressure which formerly fluctuated around 100 to 110 systolic and 60 to 70 diastolic was consistently higher: 130/90 in the first few days, 120/80 thereafter, with a resting pulse of 65 to 75.

Blood Volume.—On September 24, 1945, blood volume studies (Fig. 4) were made by Dr. James Hopper, Jr., of the University of California:

Patient's weight 58.5 kg.; height 172 cm. CO method: 6,100 cc. blood volume; 3,420 cc. plasma; 2,680 cc. cells; T 1824 dye: 6,000 cc. blood volume; 3,370 cc. plasma; 2,630 cc. cells. Packed cell volume 44 per cent. Blood serum proteins 6.8 Gm. per cent. These studies were repeated on October 23, 1945, three weeks after operation: CO method: 5,130 cc. blood volume; 3,080 cc. plasma; 2,050 cc. cells; T 1824 dye: 5,250 cc. blood volume; 3,150 cc. plasma; 2,100 cc. cells. Packed cell volume 40 per cent. Blood serum proteins 7.45 Gm. per cent.

Fluid Balance.—For the four days preceding operation the total fluid intake was 13,930 cc. with a urinary output of 11,940 cc. During the four days following operation the fluid intake totaled 6,810 cc. with a urinary output of 9,620 cc. This increased output over intake following operation is part of the readjustment and reduction in total blood volume that occurs following permanent elimination of a fistula.

Electrocardiography.—(Fig. 5) Before atropinization: pulse 71; sinus rhythm; small Q-wave in all leads; T normal; at the pulmonic area a systolic murmur. On closing the fistula, the pulse rate dropped to 41, the intensity both of the first sound and of the pulmonic murmur was decreased, but the second sound was increased; the amplitude of the brachial pulse was diminished and a plateau of high pressure appeared at once, several beats *before* the retardation in pulse.

After atropine gr. 1/50 subcutaneously: on closing the fistula retardation in

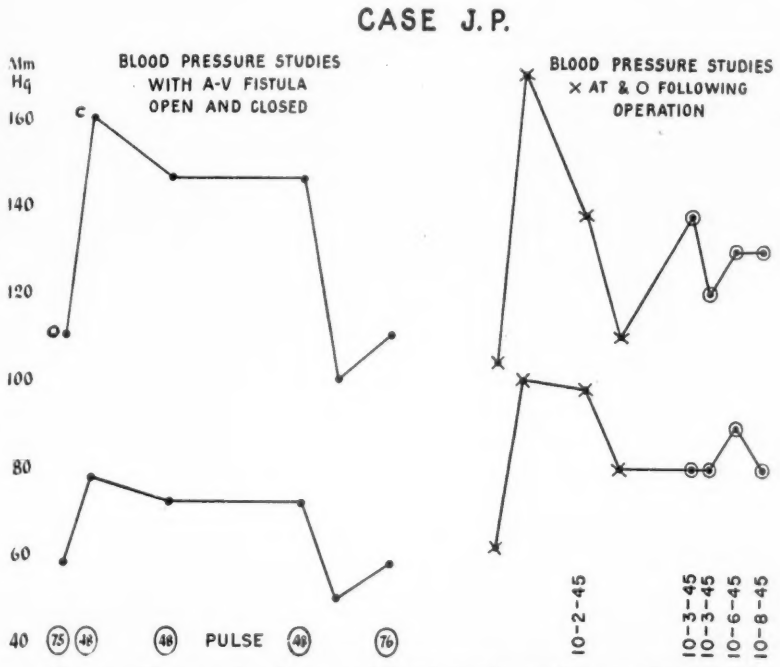


FIG. 3.—Closure of a large peripheral fistula produces a characteristic great rise in blood pressure for several beats only, subsiding promptly to a lower level of increased pressure as long as the fistula remains closed, dropping acutely when the fistula is opened, followed by prompt recovery to its usual level. The increase in pressure is accompanied by a marked retardation in pulse as long as the fistula remains closed. Following elimination of fistula by operation, the systolic pressure is temporarily elevated, the diastolic pressure is permanently increased.

pulse rate was practically absent, but the increase in blood pressure occurred as usual and the brachial pulse wave showed a diminution in amplitude and a plateau of increased pressure as before.

Teleroentgenography.—(Fig. 6) Before operation the heart measured 15.3 cm. in transverse diameter, and the aortic diameter measured 6.0 cm. Blood vessel markings in the lungs were very prominent indicating a greatly increased flow through the pulmonary vessels in the presence of the open fistula. Twenty days after operation, the heart measured 14.2 cm. in diameter and 96 days after operation, 12.3 cm.

Roentgenologic Kymography.—These studies yielded important and instructive observations. Ten-second kymograms were made, in one of which the fistula was open during the first five seconds of exposure and closed by digital pressure during the next five seconds of exposure. Another ten-second kymogram was made, in

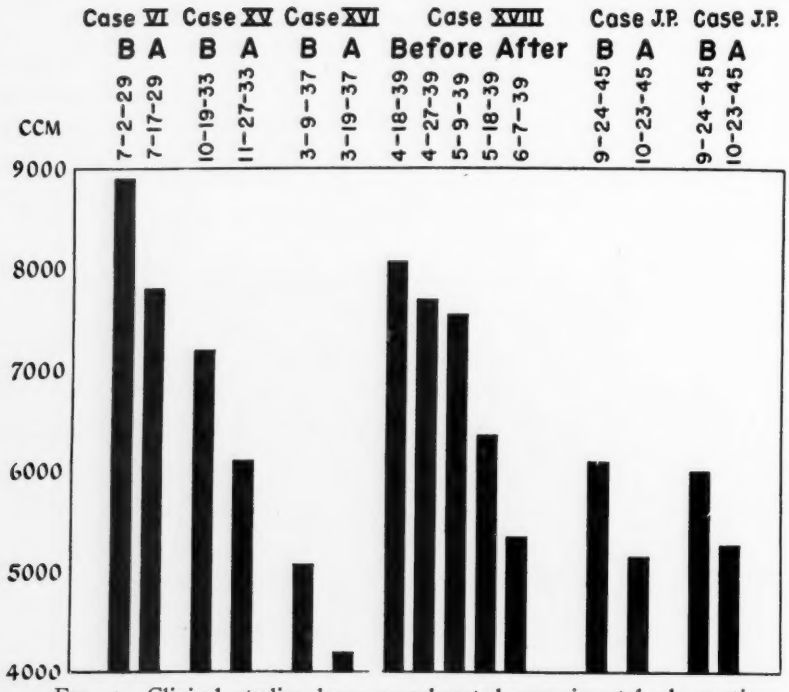


FIG. 4.—Clinical studies have corroborated experimental observations that there is a considerable increase in total blood volume in the presence of a peripheral fistula as shown by a decrease in total blood volume when the fistula was eliminated by operation: 1,000 cc. in Case 6; 1,200 cc. in Case 15; 800 cc. in Case 16; 2,700 cc. in Case 18, characterized by cardiac decompensation due to the fistula; 1,000 cc. in Case J. P.

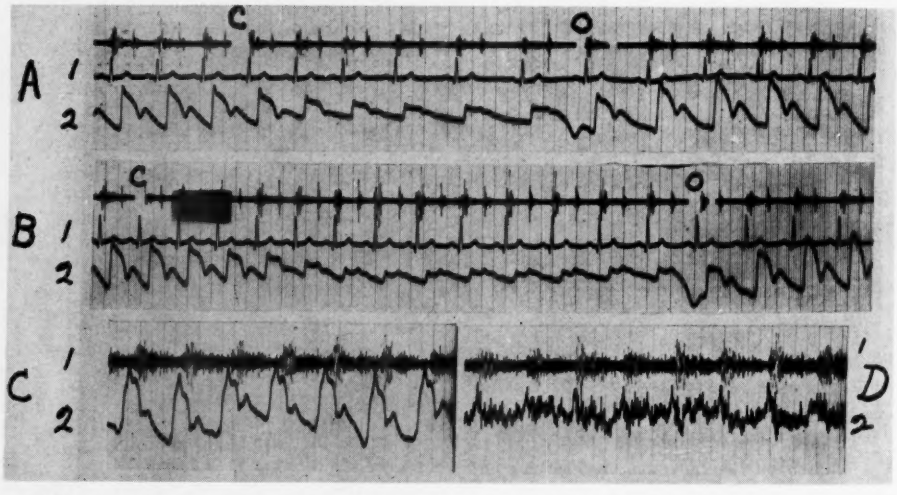


FIG. 5.—Case 1: (A) (1) Electrocardiogram, and (2) brachial pulse tracing with fistula closed at (C) and opened at (O). Brachial pulse shows prompt change in configuration on closing fistula due to increase in pressure. Retardation in pulse rate follows rise in pressure by several beats.

(B) Electrocardiogram and brachial pulse tracing following atropinization. On closing fistula brachial pulse shows prompt change in configuration due to rise in pressure but pulse is not retarded.

(C) (1) Sound-tracing of murmur at fistula showing systolic intensification. (2) Pulse-tracing of subclavian artery.

(D) (1) Sound-tracing of murmur at fistula. (2) Tracing of thrill over femoral vessels proximal to popliteal fistula.

which the fistula was closed during the first five seconds of the exposure and open during the second half of the exposure. (Fig. 7). Since the cardiac contraction rate was retarded when the fistula was closed, inspection of the kymogram enabled one to determine at a given second whether the fistula was open or closed by noting the contraction rate. A detailed study of the records obtained revealed the following variations in cardiac size depending upon conditions at the fistula (Fig. 8): Frame 1 recorded the right border of the right auricle. When the fistula was closed, the auricle was reduced in size, and when the fistula was opened the auricle was again distended.

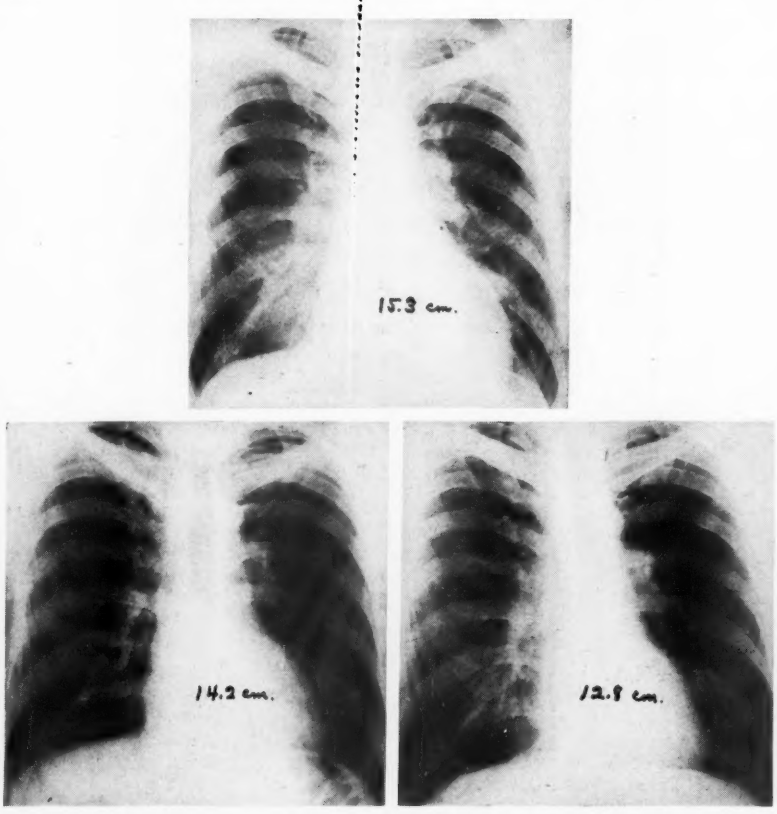


FIG. 6.—Teleroentgenograms in Case 1. (See text.)

Frame 2 recorded the left border of the descending aorta. When the fistula was closed the aorta was greatly distended, and when the fistula was opened, the aorta resumed its previous smaller size.

Frame 3 recorded the left border of the pulmonary conus. When the fistula was closed the pulmonary conus was reduced in size, and when the fistula was opened the pulmonary conus resumed its previously distended state.

Frame 4 recorded the left border of the left ventricle. When the fistula was closed the left ventricle was distended, and when the fistula was opened the ventricle decreased in size.

These variations in the size of the chambers and central vessels of the heart that follow immediately upon closing a fistula are explained as follows: Closing the fistula forces into the general arterial circulation including the

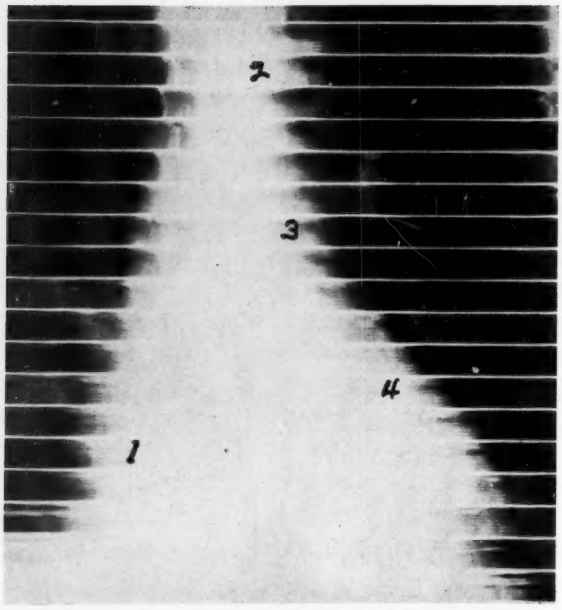


FIG. 7.—Case 1: Roentgenographic kymogram of heart in presence of popliteal fistula, which was closed by digital compression during first half of exposure and open during second half of exposure. (See Fig. 8.)

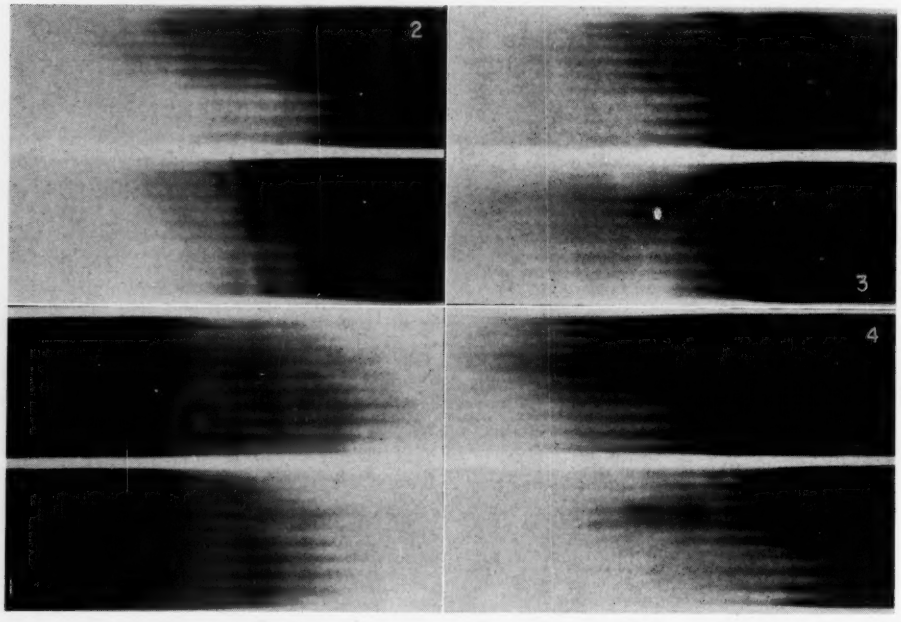


FIG. 8.—Enlargement of individual frames of roentgenographic kymogram shown in Figure 7. See text for explanation.

aorta and left heart the blood that formerly leaked through the fistula into the capacious venous system. But since the total blood volume has materially increased in the presence of the fistula its closure causes the entire arterial system to become distended with the abnormally increased blood volume which formerly coursed through the fistulous or parasitic circuit. This distention of the arterial system on closure of the fistula was disclosed by the kymographic enlargement of the aorta and left ventricle, and the reduced flow in the venous circulation was revealed in the decreased kymographic size of the right auricle and pulmonary conus.

In other cases following operation for *permanent* closure of the fistula,[26, 27] this overdistention of the already dilated heart and aorta was observed to be only temporary. The heart and the central vessels were seen to remain overdistended for approximately 24 to 36 hours. Since the need for the increased total blood volume was eliminated by the permanent closure of the fistula the total blood volume slowly diminished to normal, the volume or bulk of blood flowing through the heart was reduced to normal, resulting in an adjustment reduction also in the size of the heart itself to normal — except for a slight hypertrophy that had occurred during the life of the fistula. In numerous observations, the cardiac enlargement has been shown to be due mainly to a dilatation and to a lesser degree to hypertrophy. Even though cardiac output is greatly increased by a fistula, the stimulus to hypertrophy which this might provide is partly balanced or cancelled by the decreased cardiac effort incident to the decreased peripheral resistance and the lowered diastolic pressure imposed by the fistula.

The overdistention and then gradual reduction in cardiac size to normal following elimination of a fistula are exactly opposite to the changes that occur when a fistula is introduced into the circulation. Clinically, gradual dilatation to point of decompensation has been observed in a patient over a period of years[27] but more accurate studies of the effects of a fistula upon the heart have been made in the experimental laboratory.[27, 28] These demonstrate that the opening of a large fistula is accompanied by an immediate *decrease* in the size of the heart, due to the loss of blood from the arterial bed into the capacious venous system. This decrease, which is comparable with the reduction in cardiac size that accompanies serious external hemorrhage, is only fleeting, rarely lasting more than one or two days when the heart again returns to normal size, only to be followed by a gradual dilatation, as total blood volume is increased, and as the amount of blood flowing through the heart from the normal circulation is augmented by the volume of blood flowing through the fistulous or parasitic circuit. The rapidity of such dilatation is determined by the volume of blood short-circuited through the fistula which, in turn, is dependent upon several important variables: the size of the fistula, its location in the vascular tree, and its duration, all of which were originally stressed by Dienemann[29] as early as 1892. Much of the controversy with respect to a fistula emanates from failure to recognize the importance of these variables in producing

equally variable effects upon the circulation. Moreover, the character and type of healing that occur at the site of the fistula are also most important factors in determining the ultimate effects of a fistula upon the circulation. If fibrous tissue, rigid and inelastic, is deposited around the fistula, around the artery, or around the proximal vein, in sufficient quantity to prevent the subsequent dilatation of these structures, there will be marked limitation of the amount of blood short-circuited through the fistula and, therefore, the circulatory effects will be minimal or greatly limited. In fact, experimentally,[17] ligation of the vein proximal to a fistula completely prevented any subsequent dilatation of vessels or heart, and ligation of the artery proximal to the fistula resulted in dilatation of the artery *distal* to the fistula,[18] which is only a rare clinical observation.

The crucial factor in determining the amount of blood diverted through the fistula is the difference in peripheral resistances offered to the flow of blood in the normal circuit and in the fistulous or parasitic circuit. The nearer to the heart the fistula is located, the greater is the peripheral resistance distal to it, and also the greater is the difference between the high pressure in the artery and the absent or low pressure in the vein. This results in an easier flow of blood through the fistula than through the distal capillary bed and its high resistance. This tendency for blood to be diverted more readily through the fistulous circuit will continue so long as the resistance to its flow in this circuit is less than through the normal capillary bed. If the tissues at the site of the fistula are easily distensible, and if scar tissue is minimal, the equalization of resistances in the two circuits may be indefinitely postponed; *i.e.*, given the two possibilities of flowing through the fistula or through the capillary bed, blood will flow through the site of less resistance, which in the absence of unyielding scar tissue will be the easily distensible fistula. The increasing volume of blood flowing through the fistulous circuit because of its lessened peripheral resistance results in a gradual dilatation of all the component parts of the parasitic circulation, namely, the heart, the artery from heart to fistula, the fistula itself, and the vein from the fistula to the heart. Such a dilatation may be a very slow process, as illustrated by three clinical cases in which cardiac dilatation and decompensation took place 24, 25, and 26 years after the establishment of the fistula.[21, 26, 30] It also may occur very rapidly, as observed by Mason,[13] if the lesion is located in large vessels near to the heart.

If the fistula is small or if the scar tissue at site of the fistula is dense and unyielding, equalization of the resistances in the fistulous and normal circulations is reached soon, the volume of blood short-circuited through the fistula early reaches a stationary level, and dilatation of the fistulous circuit either will not occur or will be minimal. It is readily understood, therefore, how variable may be the effects of a fistula upon the circulation, depending in large measure upon conditions at the site of the fistula.

Retardation in Pulse on Closing a Fistula.—This highly interesting and unique phenomenon was first described in relation to an acquired

fistula by Branham,[22] but had previously been noted by Nicoladoni[1] in a congenital "phlebarteriectasie" of the right upper extremity, and by Israel[2] in a patient with congenital arteriovenous connections in the right lower leg. In each instance, occlusion of the proximal artery caused slowing of the pulse. Both Nicoladoni's and Israel's patients also exhibited greatly dilated hearts which in Israel's patient subsided to normal following amputation of the leg necessitated by gangrene which followed ligation of the femoral artery proximal to the abnormal communications.

Explanations for the occurrence of this retardation in pulse rate are few in number and in most instances are inadequate. That it is associated with the increased blood pressure that occurs on closing a fistula has been stressed by many writers. Weber[31] ascribed the increased blood pressure to the cardiac hypertrophy which he said occurred during the life of the fistula in order to maintain a normal blood pressure. On closing the fistula, the abnormally hypertrophied heart produced an abnormally increased pressure which, in turn, evoked a retardation in pulse through stimulation of the depressor nerve. He was probably the first to demonstrate that after atropinization the pulse did not slow, although the increase in blood pressure occurred as usual.

Von Bonin[32] asserted that the slowing of the pulse could not be consecutive to an increased blood pressure because the blood pressure was not always increased. He ascribed it to a chemical change, a diminution of oxygen content in the right auricle, acting upon the sinus control which during the presence of the fistula had become accustomed to an increased oxygen content of the blood.

Caro[33] thought the increased blood pressure on closing a fistula produced an increased intracranial pressure and, therefore, a stimulation of the vagus center. It is indeed a fact that every patient in whom the phenomenon of increased blood pressure and retardation of pulse is prominently exhibited, experiences a feeling of fullness of pressure in his head when the fistula is closed.

Lewis and Drury[9] explained the retardation as a vagal response to the increased blood pressure, but failed to explain the increased pressure. Indeed, few writers adequately explain the very unique but characteristic rise in pressure that follows closure of a fistula: the few beats of very high pressure followed by a drop to a lower level of increased pressure until the fistula is again opened (Fig. 3). This characteristic curve of blood pressure has been noted in numerous clinical cases and has been observed experimentally as well.[34] Examination of the pulse tracings and electrocardiogram in the present case corroborated a previous demonstration that the *first* effect of closing a fistula is the increased blood pressure and that the *second* effect is the retardation in pulse rate (Fig. 5). The present studies also corroborated previous observations[26] that atropine abolishes the retardation in pulse, but does not prevent the increase in blood pressure that occurs on closing a fistula.

The unequivocal enlargement of the aorta that occurs on closing a fistula as revealed in the present studies by the roentgenologic kymogram is highly important evidence in the explanation of this slowing of the pulse, which is invariable in the presence of a fistula large enough and of sufficient duration to produce a significant and demonstrable increase in total blood volume.[19] The slowing depends directly upon this increase in blood volume. When a fistula large enough to have produced such an increase in total blood volume is closed, the blood which formerly leaked into the vein is backed up into the arterial system, which then becomes overdistended and overfilled by the abnormally increased volume of blood. A demonstrable distention of the retinal arteries has been observed on closing a fistula[30] and now the roentgenologic kymograph has revealed a definite enlargement of the aorta on closing a fistula. The abnormal distention of the arch of the aorta in which reside the end-organs of the depressor nerve results in stimulation of these afferent vagal fibers, and an immediate slowing of the cardiac contraction rate occurs to neutralize or compensate for the excessive high blood pressure incident to overdistention of the arterial bed. The few beats of very high pressure occur before the pressure is reduced by slowing of the pulse, and before peripheral vasodilatation neutralizes part of the effect of the increased blood volume. Since blood volume cannot be immediately reduced to normal the increased pressure persists at a higher level as long as the fistula is closed depending upon the extent of the increase in blood volume. There can be no question of this intimate relationship of the retardation in pulse rate and of the increased blood pressure to the increase in total blood volume, which varies greatly depending on the variations in quantity of blood diverted through the fistula which, in turn, is determined by the variables already described.

Additional evidence supporting the importance of the increased blood volume is found in the behavior of blood pressure following permanent elimination of a fistula. The increase in systolic pressure which follows operation, (provided there is little loss of blood during the operation) soon subsides to normal as the increased blood volume is corrected. Concomitantly the retarded pulse rate again returns to normal. The permanently increased diastolic pressure following operative closure of fistula is attributed to the permanent elimination of the area of lessened peripheral resistance at the site of the fistula.

SUMMARY

Roentgenologic kymography provides important observations on the effect upon the heart and large vessels of closing a large arteriovenous fistula. The immediate effect is shown to be additional distention of an already dilated heart and aorta. This distention is due to backing up into the arterial bed the volume of blood formerly flowing through the fistula into the capacious venous bed. Since a large fistula of long duration is invariably accompanied by an increased total blood volume the entire arterial bed

including the left heart and the aorta is overdistended by this increased blood volume when the leak into the venous bed is suddenly closed. The immediate effect of such an overdistention of the arterial tree is a marked elevation of general blood pressure, which is promptly though not completely rectified by a slowing of the cardiac contractions and by a retardation in pulse rate which is unique. Its mechanism is dependent upon stimulation of the fibers of the depressor nerve in the arch of the aorta by the overdistention of this vessel on closure of the fistula. It is eliminated by atropinization of the patient, indicating its vagal origin. It is dependent entirely upon the increase in total blood volume that occurs in the presence of a fistula of large size and long duration. If the closure of the fistula is permanent, as by operation, blood pressure and pulse return to normal through gradual reduction of blood volume to normal. That the increase in blood volume and resulting circulatory effects occur in all fistulae to greater or less degree seems likely, but they are not always demonstrable in small fistulae with small increases in blood volume by present instruments of precision or by present scientific methods. In small fistulae also, these changes may be masked by other physiologic adjustments such as peripheral vasodilatation which may obviate the increase in general blood pressure when the blood volume increase is small.

BIBLIOGRAPHY

[1] Nicoladoni, Carl: Phlebarteriectasie der rechten oberen Extremität. Arch f. klin. Chir., **18**, 252, 1875.

[2] Israel, James: Angietasie im Stromgebiete der A. Tibiales antica. Arch. f. klin. Chir., **21**, 109, 1877.

[3] Stewart, F. T.: Arteriovenous Aneurism Treated by Angeiorrhaphy. ANNALS OF SURGERY, **57**, 574, 1913.

[4] Reider, W.: Herzschädigung infolge Arteriovenösum Aneurysmas. Arch. f. klin. Chir., **139**, 597, 1926.

[5] Rösler, H.: Über Herzvergrösserung bei angeborener arteriovenöser Kommunikation. Klin. Woch., **8**, 1621, 1929.

[6] Halsted, W. S.: Cylindrical Dilation of the Common Carotid Artery following Partial Occlusion of the Innominate and Ligation of the Subclavian. Tr. Am. Surg. Assn., **36**, 501, 1918.

[7] Halsted, W. S.: Congenital Arteriovenous and Lymphaticovenous Fistulae. Proc. Nat. Acad. Sci., **5**, 76, 1919.

[8] Matas, Rudolph: On the Systemic or Cardiovascular Effects of Arteriovenous Fistulae. Tr. South. Surg. Assn., **36**, 623, 1923.

[9] Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurism. Heart, **10**, 301, 1923.

[10] Smith, Carter: Circulation in Arteriovenous Aneurysm: Before and After Operation. Arch. Int. Med., **48**, 187, August, 1931.

[11] Dean, J., and Dean, J. C.: Arteriovenous Aneurysm: Its Effect on the Heart. Brief Review of Literature and Report of Case. Wisconsin Med. Jour., **33**, 587, August, 1934.

[12] Mason, J. M.: Traumatic Arteriovenous Aneurysms of Great Vessels of Neck: Observations upon Seven Cases. ANNALS OF SURGERY, **109**, 735, May, 1939.

[13] Mason, J. M., Graham, G. S., and Bush, J. D.: Early Cardiac Decompensation in Traumatic Arteriovenous Aneurysm. ANNALS OF SURGERY, **107**, 1029, June, 1938.

[14] Osler, William: Remarks on Arteriovenous Aneurysm. Lancet, **1**, 949, 1915.
[15] Reid, Mont R.: The Effect of Arteriovenous Fistula upon the Heart and Blood Vessels. Johns Hopkins Hosp. Bull., **31**, 43, 1920.
[16] Reid, Mont R.: Studies on Abnormal Arteriovenous Communications, Acquired and Congenital. Arch. Surg., **10**, 601, March, 1925; *idem, ibid.:* **10**, 996, May, 1925; *idem, ibid.:* **11**, 25, July, 1925; *idem, ibid:* **11**, 237, August, 1925.
[17] Holman, Emile: Experimental Studies in Arteriovenous Fistulas. III. Cardiac Dilatation and Blood Vessel Changes. Arch. Surg., **9**, 856, November, 1924.
[18] Holman, Emile: Arteriovenous Fistula: Dilatation of the Artery Distal to the Abnormal Communications; An Unusual Feature Experimentally Explained. Arch. Surg., **18**, 1672, April, 1929.
[19] Holman, Emile: Experimental Studies in Arteriovenous Fistulas. I. Blood Volume Variations. Arch. Surg., **9**, 822, November, 1924.
[20] Herrmann, G. R., and Gage, I. M.: Cardiac Hypertrophy in Arteriovenous Aneurysm. Proc. Soc. Exp. Biol. & Med., **25**, 767, June, 1928.
[21] Holman, Emile: The Physiology of an Arteriovenous Fistula. Arch. Surg., **7**, 64, July, 1923.
[22] Branham, H. H.: Aneurismal Varix of the Femoral Artery and Vein following a Gunshot Wound. Internat. Jour. Surg., **3**, 250, November, 1890.
[23] Holman, Emile: War Injuries to Arteries and Their Treatment. Surg., Gynec. and Obst., **75**, 183, August, 1942.
[24] Henle, A.: Discussion on Test for Collateral Circulation before the Forty-first Congress of the "Deutsche Gesellschaft für Chirurgie." Verh. deutsch. Gesellsch. f. Chir., **41**, 134, 1912.
[25] Coenen, H.: Zur Indikationsstellung bei der Operation der Aneurysmen und bei den Gefässverletzungen. Zentralbl. f. Chir., **40**, 1913, December 13, 1913.
[26] Holman, Emile: Arteriovenous Aneurism. ANNALS OF SURGERY, **80**, 801, December, 1924.
[27] Holman, Emile: Clinical and Experimental Observations on Arteriovenous Fistulae. ANNALS OF SURGERY, **112**, 840, November, 1940.
[28] Holman, Emile: The Anatomic and Physiologic Effects of an Arteriovenous Fistula. Surgery, **8**, 362, August, 1940.
[29] Dienemann, Franz: Ein Beitrag zur Kasuistik der arteriellvenosen Aneurysmen. August Vollrath's Hofbuchdruckerei, Erlangen, 1892.
[30] Holman, Emile: Arteriovenous Aneurysm. Surg. Clin. of No. Am., **8**, 1413, December, 1928.
[31] Weber, Arthur: Beobachtungen am traumatischen Aneurysma arteriovenosum. München. med. Wchnschr., **64**, 409, 1917.
[32] Von Bonin, G.: Über Pulsverlangsamung bei arteriovenosen Aneurysmen. Bruns' Kreigschirurgische Hefte, Bd. II (Bruns' Beiträge, **109**, 289, 1918).
[33] Caro, Dr.: Blutdrucksteigerung und Pulsverlangsamung bei Kompression traumatischer Aneurysmen. Mitt. a.d. Grenzgeb. d. Med. u. Chirur., **29**, 355, 1916-17.
[34] Holman, Emile: Arteriovenous Aneurysm. The Macmillan Co., New York, November, 1937.

DISCUSSION.—DR. DANIEL C. ELKIN, Emory University, Ga.: There has been considerable controvery for a number of years about the question of blood volume in the presence of an arteriovenous fistula. At the Ashford General Hospital we made observations on the blood volume in 40 patients with this condition. The plasma volume was determined by the use of the blue dye T–1824. The total blood volume was calculated from the plasma volume and hematocrit reading. Following removal of the fistula almost one-half of the patients showed a significant decrease in blood volume, some as much as 1,000 cc. per square meter of body surface. In general,

the greatest increases in blood volume were observed in patients who had fistulae in the larger vessels, such as the femoral and iliac. All this merely confirms what Doctor Holman has claimed for many years.

DR. RUDOLPH MATAS, New Orleans, La.: All workers in the surgery of arteriovenous aneurysms are Doctor Holman's debtors for his fundamental researches in this field. In this very valuable paper he has fully confirmed his original interpretation of the dilation of the heart and aorta, following the establishment of an arteriovenous communication and the Nicoladoni-Branham bradycardiac syndrome, with restoration to normal that follows its closure.

DR. EMILE HOLMAN, San Francisco, Calif. (closing): It may well be asked why dilatation and the bradycardiac reaction do not occur in all fistulae. They depend on the amount of blood flowing through the fistula, and we believe this is determined by the gradual dilatation of the fistula over a period of years. We found that in this instance the fistula had a diameter of 2 to 2.5 cm., whereas the original artery was no larger than 8 mm. The fistula dilated as the shorter circuit increased in size. Certain fistulae, however, do not dilate because of fibrous tissue deposited around the fistula which prevents its dilatation. Dilatation of the fistula, therefore, does not occur in all instances, depending upon the amount of scarring at the site of the fistula, and as a result of progressive dilatation of the heart also, does not occur in all instances.

BOOK REVIEW

SURGICAL TREATMENT OF THE NERVOUS SYSTEM. By F. W. Bancroft and C. Pilcher. J. B. Lippincott Company, Philadelphia, Pa. 1946.

PILCHER has done neurosurgery a distinct service by collecting together in a single book definitive articles by recognized authorities on all the many angles involved in modern neurosurgery. Those of us who are old enough can remember when a neurosurgeon concerned himself only with brain and spinal cord tumors, trifacial neuralgia and focal epilepsy. Now the surgery of the sympathetic nervous system, of ruptured intervertebral disks, of athetosis and dystonia, and of hydrocephalus are included. Of particular value and importance is the emphasis placed upon peripheral nerve injuries by devoting an entire section to this subject which was well nigh forgotten between wars.

A new group of neurosurgeons is coming forward, some of them trained only in the care of battle casualties. To these men in particular this well-rounded reference book to all facets of their specialty will be of value. And to any neurosurgeon, young or experienced, this volume will be a source of valuable information. The older men may not agree with all they find here, but in agreement or not, they must admit that the methods outlined are sound and set forth by authors of wide experience. An important chapter bringing up to date the most recent advances in chemotherapy and its value in neurosurgery is included.

The print is good, the bibliographies adequate and typographic errors few and far between. The illustrations are the only unfortunate part of this book. Some of them, especially those in the chapters dealing with the sympathetic nervous system, peripheral nerves and the spinal cord are as fine as any we have ever seen. But others, particularly artists' sketches of the various intracranial lesions are simply very bad.

This is a highly satisfactory book which it was a pleasure to review. Every younger neurosurgeon should make an effort to include it in his library. A careful study of its contents will be very rewarding.

FRANCIS C. GRANT, M. D.

ARTERIOVENOUS ANEURYSM OF THE VERTEBRAL VESSELS*

REPORT OF TEN CASES

DANIEL C. ELKIN, M.D., AND M. H. HARRIS, M.D.

ATLANTA, GA.

FROM THE VASCULAR SURGERY CENTER, ASHFORD GENERAL HOSPITAL, WEST VIRGINIA, AND THE WHITEHEAD DEPARTMENT OF SURGERY, EMORY UNIVERSITY, GEORGIA.

THE MANY VASCULAR INJURIES resulting from wounds received in the recent war have given rise to an unprecedented number of arteriovenous fistulae and aneurysms. At the Ashford General Hospital approximately 500 operations have been performed for these conditions. Ten of these were arteriovenous fistulae of the vertebral vessels in their cervical or extracranial course. It is the purpose of this communication to report these cases and in so doing to review the anatomy of the vessels, the diagnosis of the lesion, and to suggest operative methods of approach and treatment based on this experience.

Reports of arteriovenous aneurysms of the extracranial portion of the vertebral vessels are rare, and have in most instances been concerned with the recording of an experience in the treatment of one case. However, Matas,[1] in 1893, collected 19 cases from the literature and included one of his own. In addition, Perrig[2] collected 60 instances of vertebral aneurysms, but in some of these the diagnosis was open to question. Recently, Heifetz,[3] in reporting a case of his own, collected the literature on this subject, and from his excellent review it would appear that somewhat less than 100 instances have appeared in literature. Moreover, in these reports the differentiation between arteriovenous fistulae and false arterial aneurysms is not clearly brought out. Undoubtedly this number does not represent the true incidence of the condition, since single cases, particularly if ending fatally, are not so apt to be reported. At any rate, it remains among the rarest of arterial injuries, probably because of the anatomic location of the vessels.

The mortality in previous reports, either as a direct consequence of the lesion or its treatment, appears to be above 50 per cent, far higher than that of aneurysms or arteriovenous fistulae in any other location. Here, again, the anatomic position of the vessels is undoubtedly a contributing factor because of the difficulties attendant upon the operation.

ANATOMY

The extracranial portion of the vertebral artery lies deep in the neck. For descriptive purposes it is divided into three parts: The *first portion* which runs from its origin in the subclavian artery to the foramen in the

* Read before the American Surgical Association, April 2–4, 1946, Hot Springs, Virginia.

transverse process of the sixth cervical vertebra; the *second portion* which runs through the foramina in the transverse processes of the upper six cervical vertebrae; and, the *third portion* which consists of that part of the vessel from its exit from the foramen in the atlas until it enters the skull through the foramen magnum (Fig. 1).

It is important to remember that the vertebral artery is the *first branch* given off by the subclavian artery. It springs from the upper posterior

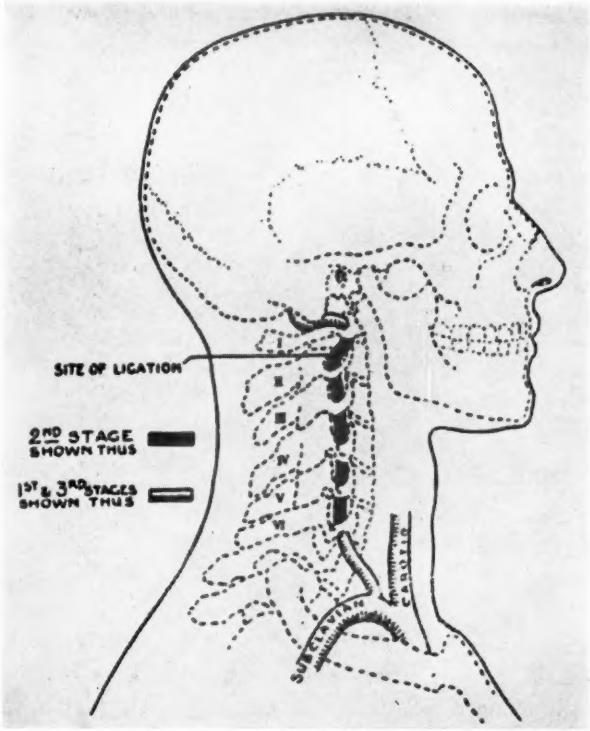


FIG. 1.—Diagrammatic representation of the first, second and third portions of the vertebral artery. The second portion is shown in black. (From Henry).

aspect of the first portion of that vessel just lateral and posterior to the common carotid artery and about .5 cm. from the medial margin of the anterior scalene muscle. This muscle is a guide to the artery. The thyrocervical trunk arises from the upper portion of the subclavian just distal to the vertebral, and because of their close approximation they may be mistaken for each other unless careful dissection is employed.

The *first part* runs upward and backward between the longus colli and anterior scalene muscles. Behind it is the transverse process of the seventh cervical vertebra and the sympathetic chain. In front of it is the vagus nerve, the internal jugular vein, and in front of this vein, the sternomastoid muscle. The upper portion of this part is crossed by the inferior thyroid

artery as it passes medially. The vessel *does not* enter the foramen in the transverse process of the seventh cervical vertebrae, but as previously stated, lies in front of it.

As the *second part* passes upward through the transverse processes of the upper six cervical vertebrae it lies anterior to the cervical nerves and beneath the anterior scalene muscle. In this portion it is surrounded by a venous plexus which terminates below in the vertebral vein. Overlying the vessel and slightly to its medial side is the internal jugular vein and more superficially the sternomastoid muscle. In the upper part of the second portion the spinal accessory nerve is found about two fingerbreadths below the mastoid process. Deep to the sternomastoid muscle the dense prevertebral fascia covers the levator scapulae muscle. This muscle arises from the transverse processes of the upper four cervical vertebrae and, therefore, directly overlies the vertebral vessels in their course through the upper four foramina.

The *third part* begins at the point where the vessel emerges from the foramen of the atlas. It turns backward and lies in a groove on the upper surface of that bone. Here the vessel is covered by the semispinalis capitis in the suboccipital triangle. The guide to the upper portion of the vessel is the transverse process of the atlas which can easily be palpated one fingerbreadth below and one in front of the tip of the mastoid bone. It is more easily identified when the sternomastoid muscle is detached from its origin, as will be discussed below.

DIAGNOSIS

Of all the aneurysms and fistulae in the body the diagnosis of those of the vertebral vessels is the most difficult to make. It was made with certainty in only five patients in this series, although it was suspected in others. It is likely to be confused with more common lesions in this region, particularly fistulae between the internal jugular vein and branches of the external carotid artery. It may also be confused with fistulae arising from other branches of the subclavian artery, particularly the inferior thyroid, the transverse scapular and transverse cervical vessels. Since the common carotid lies moderately superficial in the neck where it can be occluded by digital pressure, the bruit of fistulae arising from branches of this vessel are usually obliterated with ease. *If the bruit does not disappear on compression of the common carotid artery the vertebral vessels should be suspected as the site of the lesion.* Since the vertebral vessels lie deep in the neck, obliteration of the bruit is difficult to obtain by pressure.

OPERATION

The approach to any portion of the vertebral vessels is a difficult one because of its deep position and because of the vital nature of its surrounding structures. Since the anatomy of the three parts varies greatly, the approach to the vessels in these regions will be considered separately.

In the first portion it can best be reached through an incision parallel

to the fibers of the sternomastoid muscle and directly over the interval between the sternal and clavicular heads of that muscle. After the deep fascia is incised, the two heads of the muscle are separated and retracted (Fig. 2). If necessary to obtain better exposure no harm is done by transversely dividing some of the fibers of this muscle. When the internal jugular vein is

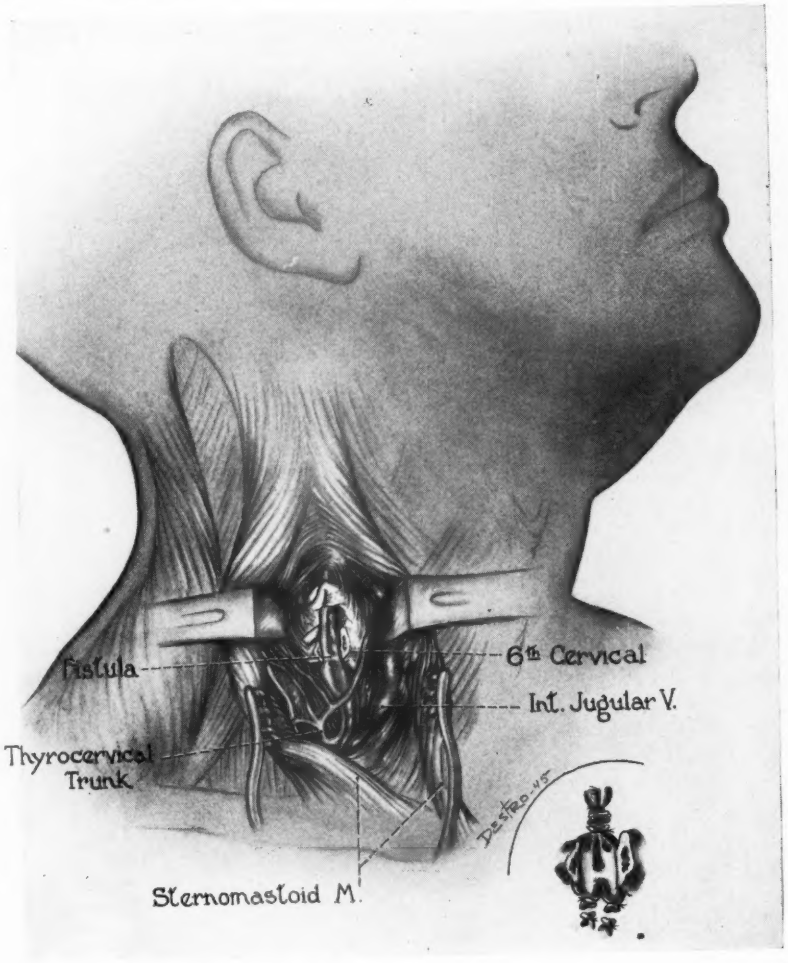


FIG. 2.—The approach to the first portion and the lower part of the second portion of the vertebral vessels.

encountered in the depth of the incision it is retracted medially and the triangular interval between the longus colli and the anterior scalene muscles is developed. The inferior thyroid artery will be found running upward and medially and crossing in front of the vertebral artery in this region, and the two must be carefully isolated. On the left the thoracic duct passes in front of the artery. The vertebral artery arises medial to the inferior thyroid and in this location can be identified by its pulsation. The vertebral

vein lies anterior to the artery. This portion of the vertebral artery should always be identified as a preliminary step in operations on the vessel elsewhere in its course. A ligature passed around the vessel, but not tied, serves as a protection should hemorrhage occur later in the operation. It should be remembered, however, that there is a rich anastomotic blood supply in the vertebral system, and that ligation of the proximal artery will only diminish and not control hemorrhage. Ligation at this point in the operation should

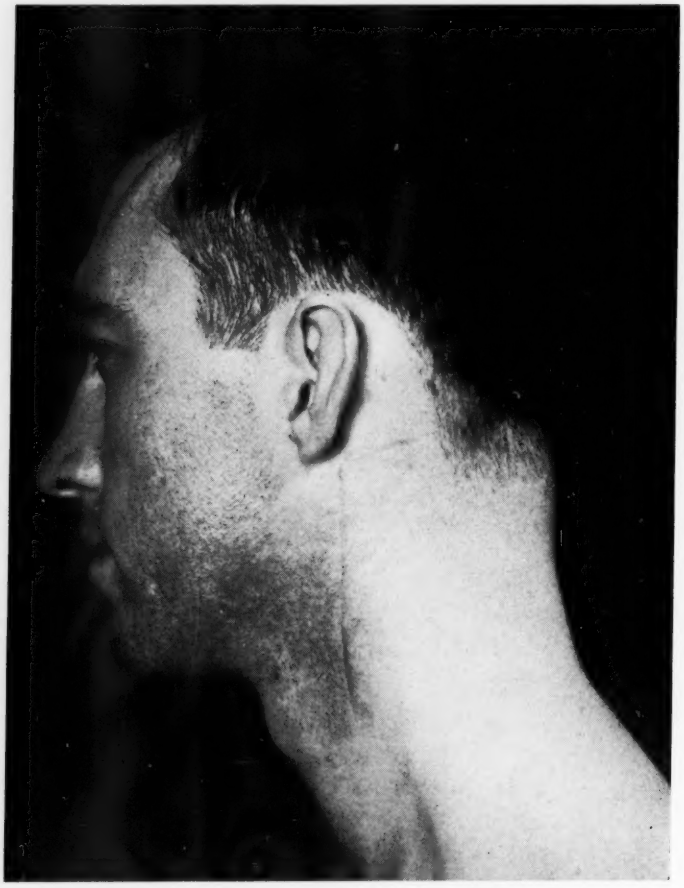


FIG. 3.—The incision for exposure of the third portion of the vertebral vessels.

not be done since it will obliterate the thrill and bruit, thus, making identification of the fistula more difficult.

The second portion of the vessel is reached by an incision along the anterior border of the sternomastoid muscle. When the deep fascia is opened the muscle is retracted laterally and the carotid sheath identified and retracted medially. It is usually necessary to divide the omohyoid muscle as it passes across the carotid sheath. The anterior scalene muscle which arises from the transverse processes of the third, fourth, fifth, and sixth

cervical vertebrae is retracted laterally and, if necessary, may be detached from its origin to fully expose the transverse processes through which the vertebral vessels pass. The interval between the transverse processes is less than a fingerbreadth, and ligation in this region is particularly difficult unless one or more of the transverse processes is removed by rongeur. When this is done a ligature may be passed, preferably on an aneurysm needle, about the vessel or it may be occluded by the use of heavy metal clips.

Exposure of the upper portion of the second part and of the third part of the vertebral vessels is by far the most difficult. Henry[4] has described a

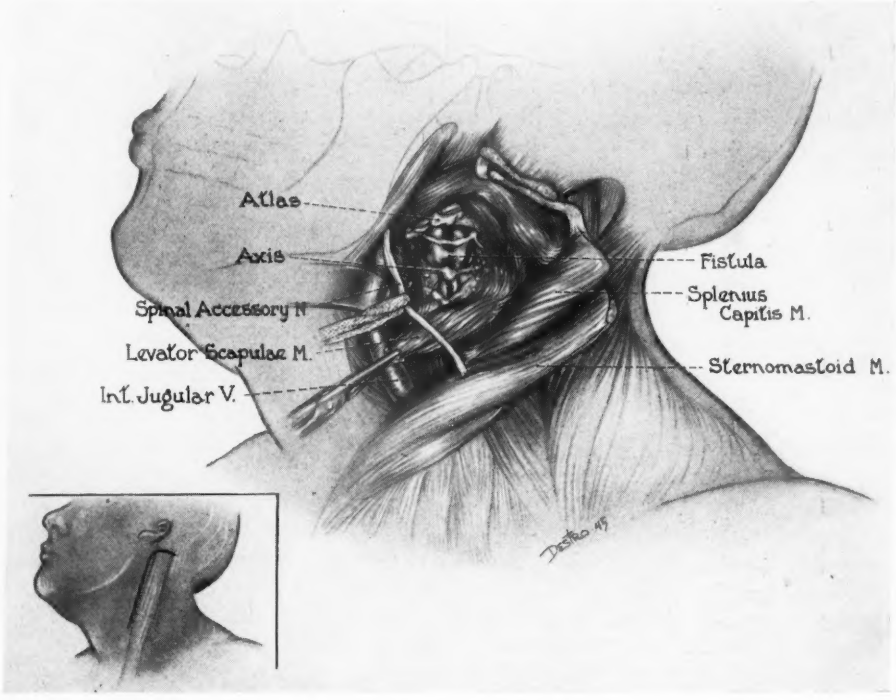


FIG. 4.—The exposure of the upper portion of the vertebral vessels.

method of approach for the purpose of ligating this portion of the vessel which we have successfully employed in four instances (Cases 3, 6, 9 and 10). The patient lies on his back with the neck extended and the chin turned to the side opposite the involved vessels. An incision is made along the anterior border of the sternomastoid muscle from the middle of the neck to the mastoid process (Fig. 3). The deep fascia is opened and the insertion of the sternomastoid is cut away from the bone and the muscle reflected laterally. The spinal accessory nerve is isolated and mobilized as it passes laterally and downward beneath the sternomastoid muscle (Fig. 4). With the reflection of the muscle the tip of the transverse process of the atlas is easily identified. The prevertebral fascia is divided from above downward

and the origin of the levator scapulae muscle is cut away from the atlas and axis and turned downward. Further dissection will expose the vertebral artery and surrounding venous plexus in the interval between the atlas and axis, as well as in its third portion.

The fistula in all the cases of this series was produced by trauma. In nine patients it was due to direct injury of the vessels by a missile, usually a small fragment of high explosive shell. In one instance (Case 6), there was no penetrating wound and the fistula followed severe external trauma caused by a blow from a piece of wood. In none was there a fracture of the transverse process of the vertebra discernible by roentgenogram, but this type of injury should be borne in mind as a possible cause of the condition.

In the ten cases here reported the lesion was located in the first portion of the vessel in one instance, in the second portion in six instances, and in the third portion in three instances. In none was any attempt made to repair the fistula. The position of the vessels as well as their small size will preclude any effort of repair. Its anatomic position prevented actual excision of the fistula except in three instances (Cases 1, 2 and 8), and, therefore, its obliteration was usually accomplished by proximal and distal ligation of the vessels and the placing of mass ligatures. It is to be stressed that complete control of the blood supply is necessary for the prevention of hemorrhage. One should not hesitate to remove the transverse processes of the cervical vertebrae in order to completely expose the lesion and its contributing vessels.

REPORT OF CASES

CASE 1.—*A-V fistula, left vertebral vessels, upper third, due to bullet wound November 10, 1942. Excision of fistula through suboccipital approach, June 15, 1943. Secondary hemorrhage controlled by ligation of the vertebral artery and packing wound. Cured.*

On November 10, 1942, this soldier was struck in the left malar region with a 44-caliber bullet. The missile traversed the face, the lateral aspect of the neck, and became imbedded in the soft tissues of the left occipitomastoid region. There was no extensive external hemorrhage, but the tissues of the left side of the neck swelled considerably. Within a few days he noticed a loud buzzing in his left ear. Upon occasion his pulse rate would become rapid. On December 22, 1942, the bullet was removed, and on February 22, 1943, the left common carotid artery was ligated without change in his symptoms.

On admission to the Ashford General Hospital, two months later, there was a small scar over the left malar region; the wound of entry. There was an operative scar 4 cm. mesial to the tip of the left mastoid. The tissues in this region appeared full in comparison to those on the right. Palpation revealed a deeply situated pulsating mass with a distinct systolic thrill. On auscultation, a continuous bruit accentuated in systole with maximal intensity over the occiput could be heard. This could be obliterated by deep pressure over the sternomastoid muscle. Arterial pulsation was absent over the left common carotid artery, the site of the earlier ligation. It was thought that this was an arteriovenous fistula of the cirsoid type, probably involving the occipital artery and vein deep to the muscles and posterior to the mastoid process. The question of involvement of the vertebral artery with accompanying veins in this region was considered.

An excision of these vessels was carried out June 15, 1943. A semicircular incision beginning over the left mastoid muscle was carried upward over the base of the skull to the midline. The deep muscles were cut and retracted caudally. The external carotid artery was ligated; however, this had no effect upon the aneurysm which could be seen and felt at the base of the skull. The aneurysm was excised by ligating and cutting numerous arteries and veins which could be seen to communicate with vessels entering the skull. Considerable bleeding was encountered which was controlled by coagulation and by the use of fine silk ligatures. At the end of the operation the bruit and thrill had disappeared.

Two weeks later, as a result of a friendly wrestling match, the wound was opened and severe secondary hemorrhage occurred. This was controlled by hemostats, which were left in place, and by packing. Following this the vertebral artery was ligated in its first portion, which apparently controlled the bleeding since no further hemorrhage occurred with removal of the clamps and packing five days later. The wound healed uneventfully. There was no return of the bruit and thrill upon discharge three months later and upon review examination three months after discharge.

CASE 2.—*A-V fistula, left vertebral vessels, upper third, due to shell fragment wound September 14, 1943. Ligation of left vertebral artery January 20, 1944, with improvement. Partial excision of fistula February 2, 1944. Complete excision April 20, 1944. Cured.*

On September 14, 1943, this soldier was struck in the left side of the face by a fragment of high explosive shell. The wound of entrance was just anterior to the left ear and there was no wound of exit. He was unconscious for approximately three hours after the injury. There was considerable bleeding from the wound. On regaining consciousness he noticed impairment of hearing on the left with numbness and weakness of the left side of the face. On the following day he developed an occipital headache and diplopia which persisted for nine days. The left side of the face became markedly swollen. On admission to the Ashford General Hospital, four months later, there was a paralysis of the left side of the face, impairment of hearing of the left ear with narrowing of the left external auditory canal and the left ear drum completely replaced by granulation tissue. A continuous bruit and thrill were present over the left side of the face and neck, with maximum intensity in the occipital region. An expansile pulsation was noted in this region. A metallic foreign body was present at the tip of the spinous process of C-1 on the left. A diagnosis of arteriovenous fistula of the vertebral vessels was made.

On January 20, 1944, the external carotid artery and the first portion of the vertebral artery on the left were ligated. There was a definite decrease in the bruit when the vertebral artery was ligated. On February 2, 1944, an attempt was made to excise the arteriovenous fistula. A 10-cm. longitudinal incision was made from the skull downward along the posterior border of the sternomastoid muscle. After opening the deep fascia a large plexus of arteries and veins, in which a thrill could be felt, was disclosed. The veins were dilated and friable, and they, together with a mass of arteries, were individually isolated, ligated, and removed. It was felt that further extension of the aneurysm might be present in the deeper structures, but continuation of the procedure at that time was not justified as it was hoped that a cure had been accomplished from this procedure. Following operation the bruit was markedly diminished but was still audible. On April 13, 1944, the right vertebral artery was ligated. On April 20, 1944, an incision was made through the old scar along the posterior border of the sternomastoid muscle. Deep in the wound a pulsating mass could be felt which was in the vertebral vessels between their exit from the transverse process of the first cervical vertebra and their entrance into the skull through the foramen magnum. This position made the approach extremely difficult since there was no means of isolating the blood vessels. However, the mass was exposed, the vertebral vessels at the base of the skull were clamped, and the fistula was excised. The vessels were ligated with silk

with considerable difficulty and one vessel which split to the foramen magnum was sutured after the hemorrhage was controlled by finger pressure. This was done by passing three silk ligatures under the finger. When the mass was removed no further bruit or thrill was heard or felt. The postoperative course was uneventful. There was no recurrence of the bruit or thrill at the time of discharge two months later.

CASE 3.—*A-V fistula, left vertebral vessels, second portion, due to shell fragment wounds June 28, 1944. Ligation of vertebral artery in the first portion, December 30, 1944, with improvement. Ligation of the vertebral artery between atlas and axis, February 3, 1945, with further improvement. Removal of transverse processes of third and fourth cervical vertebrae and mass ligation of fistula, April 25, 1945. Cured.*

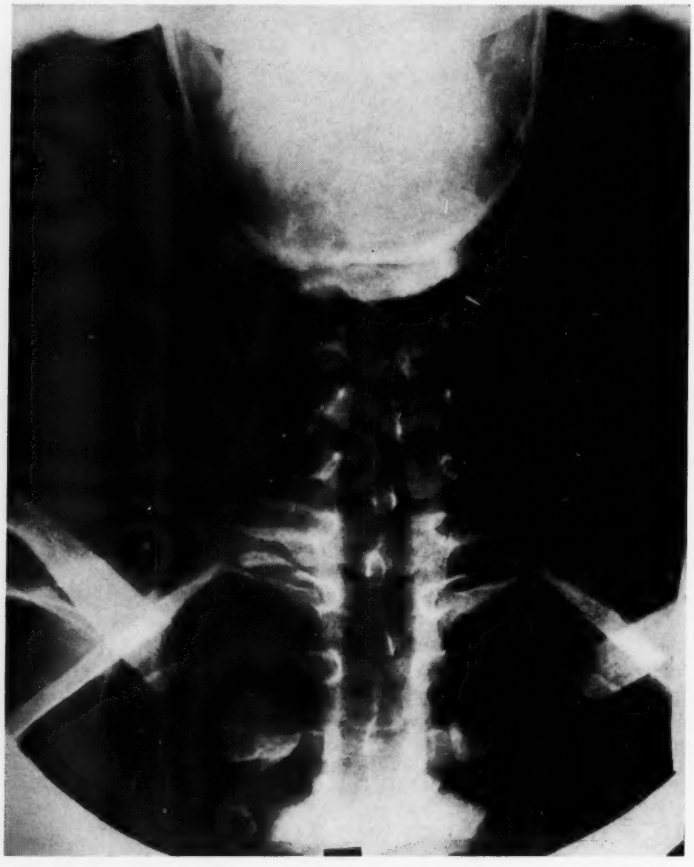


FIG. 5.—Case 3: Silver clip on the upper portion of the vertebral artery.

On June 28, 1944, this soldier was struck in the right arm and neck by multiple fragments of an artillery shell. There was profuse bleeding from all wounds. The neck wound was débrided and healed promptly. Approximately three weeks later he noted a buzzing sensation in the left side of the neck but did not hear any noise. He reported this to his medical officer who made a diagnosis of arteriovenous fistula. On admission to the Ashford General Hospital, five months later, there was a small scar overlying the upper portion of the left sternomastoid muscle about 4 cm. below the angle of the mandible. There was a continuous bruit and thrill heard and felt over this area, which

were transmitted up the scalp to the parietal region and into the neck to the clavicle. Deep pressure failed to obliterate the bruit and thrill. It was thought that this was an arteriovenous fistula of the second portion of the left vertebral vessels. On December 30, 1944, the first portion of the vertebral artery was ligated and divided. This caused the thrill and bruit to be almost completely obliterated. On February 3, 1945, an incision was made from the level of the thyroid cartilage upward along the anterior border of the sternomastoid muscle to the mastoid process and then turned backward severing the sternomastoid from the skull at its insertion. The muscle was retracted laterally and the third cervical nerve and the spinal accessory nerve were isolated. The levator scapulae muscle was detached from its origin from the atlas, axis, and third and fourth cervical vertebrae. The vertebral vessels were then isolated between the transverse processes of the atlas and axis. The sensory branch of the second cervical nerve overlying the vessels was dissected free and the vertebral artery was divided between ligatures. Several smaller vessels in this region were also ligated. The vein was not ligated. This stopped the thrill but a bruit was still present.

The bruit increased in intensity and, April 25, 1945, the scar on the left side of the neck was excised and the sternomastoid muscle retracted laterally. The transverse processes of the first, second, third, and fourth vertebrae were exposed. The levator scapulae muscle was detached from the transverse process of the atlas and the spinalis group of muscles freed from the transverse processes of the above vertebrae by sharp and blunt dissection. The lateral roofs of the foramina transversarium of the third and fourth cervical vertebrae were removed by rongeur. This exposed the vertebral vessels for a distance of 4 or 5 cm. The fistula was apparently at the level of the inferior border of the canal of the third vertebra. Ligatures were passed about the vessels proximal and distal to the fistula and the vessels ligated. Silver clips were applied above and below the fistula (Fig. 5). This caused the bruit and thrill to completely disappear. There was no recurrence of the bruit or thrill at the time of discharge three months later.

CASE 4.—*A-V fistula, right vertebral vessels, second portion, due to rifle bullet wound September 15, 1944. Removal of transverse process of sixth cervical vertebra. Mass ligation of vertebral vessels, January 16, 1945. Cured.*

On September 15, 1944, this soldier was struck in the right side of his neck by a rifle bullet. The wound of exit was in the anterior aspect of the left infraclavicular region. There was profuse bleeding from the right side of the neck, which was controlled by pressure. On September 17, 1944, the wound of the left shoulder region was débrided and a plaster splint applied because of a fracture of the left clavicle. Several weeks later a pulsating mass in the right side of the neck was discovered. The wound on the right healed without difficulty. On admission to the Ashford General Hospital, five weeks later, there was a healed wound, about 3 cm. in length, on the right side just above the clavicle. There was also a granulating wound in the left infraclavicular region. There was a continuous bruit and thrill in the anterior triangle of the right side of the neck, which was transmitted along the course of the carotid vessels and was audible in the chest. Upon obliteration of the fistula the pulse fell from 84 to 76 and the blood pressure in the right brachial artery rose from 160/90 to 160/110. It was thought that this was an arteriovenous fistula of the right common carotid artery and internal jugular vein. On January 16, 1945, a longitudinal incision was made on the right from the clavicle to the level of the thyroid cartilage. The incision was extended between the two heads of the sternomastoid muscle and the common carotid artery and internal jugular vein were isolated. There was no evidence of a fistula present in this region and as pressure beneath the clavicle caused the bruit and thrill to disappear it was felt that the fistula was at a more proximal point. The lower end of the incision was then extended laterally over the clavicle and the proximal third of this bone resected subperiosteally. Isolation of the common carotid artery to the innominate revealed no evidence of a fistula. It was then discovered that the fistula involved the

vertebral vessels at a point near the bony canal of the sixth cervical vertebra. The carotid artery and internal jugular vein were retracted medially and the vertebral vessels isolated to the point where they passed into the foramen transversarium of the sixth cervical vertebra. Occlusion of the artery at this point caused the thrill to disappear but the bruit was still audible. The lateral roof of the foramen transversarium of the sixth cervical vertebra was removed by rongeur, and occlusion of the vessels just proximal to the fifth cervical vertebra did not cause the thrill to disappear. The artery and vein proximal to the fistula were doubly ligated, transfixed and divided. Ligatures were passed about the vessels distal to the fistula in the space between the

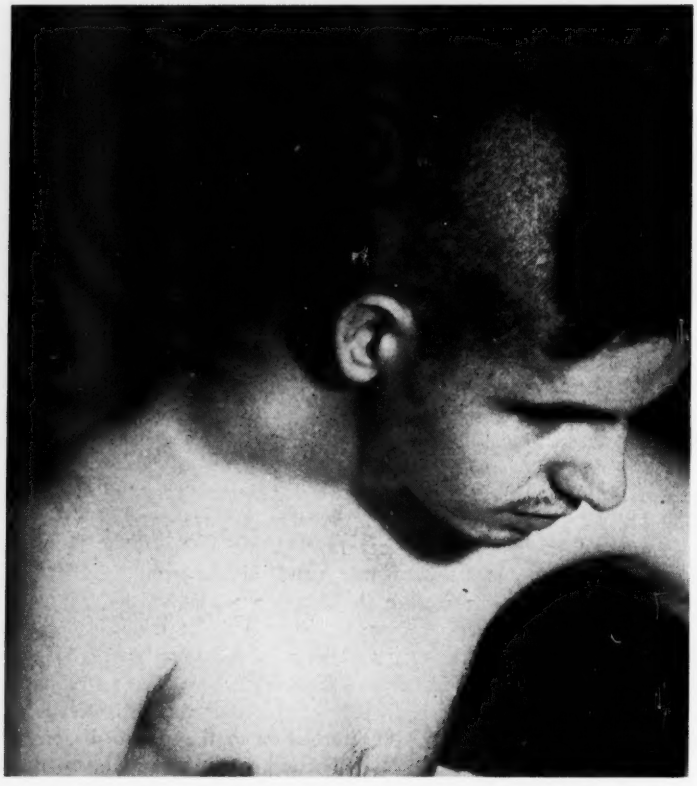


FIG. 6.—Case 5: Swelling of the neck produced by false sac of vertebral arteriovenous aneurysm.

fifth and sixth vertebrae and the vessels doubly ligated. There was moderate hemorrhage from the venous plexus extending into the spinal canal, which was controlled by pressure and muscle packing. The bruit and thrill completely disappeared. The wound healed without difficulty. The bruit and thrill had not recurred at the time of discharge four months later.

CASE 5.—*A-V fistula, with false sac, right vertebral vessels, second portion, due to shell fragment wounds January 14, 1945. Ligation of vertebral artery in first portion, and intrasaccular closure of fistula with sutures and silver clips, March 13, 1945. Cured.*

On January 14, 1945, this soldier was struck in the right shoulder, neck, and the left side of back by multiple fragments of a high explosive shell. There was no loss of consciousness and he was able to walk about after injury. About two weeks later he noted a swelling in the lower posterior aspect of the right side of his neck. Ex-

amination revealed the presence of a continuous bruit and a pulsating mass in this region. On admission to the Ashford General Hospital two months later there was a fusiform, firm swelling in the posterior aspect of the right side of the neck (Fig. 6). No thrill could be felt in this region, but a continuous bruit was heard along the anterior and posterior borders of the mass. The bruit could not be obliterated by occlusion of the common carotid artery low in the neck. It was thought that this was an arteriovenous fistula, with false sac, possibly involving the transverse cervical or the vertebral vessels.

On March 13, 1945, a preliminary incision was made just above the clavicle and the clavicular portion of the sternomastoid muscle divided. The transverse cervical

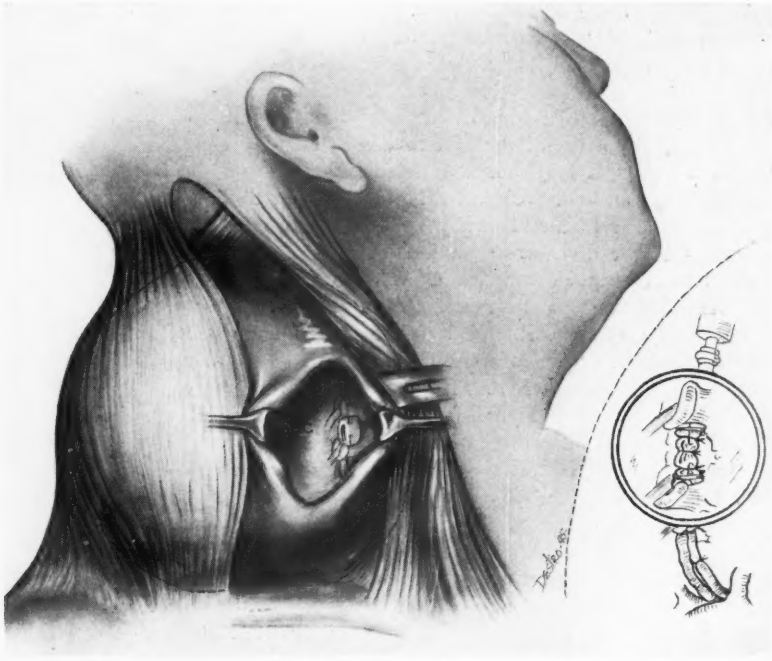


FIG. 7.—Case 5: Exposure of the vertebral vessels by incision through the false sac. Insert shows obliteration of the fistula by clips and mass ligatures.

artery was ligated, which had no effect upon the bruit. The anterior scalene muscle was divided, exposing the subclavian artery. Occlusion of the vertebral artery caused the bruit to disappear. A "bulldog" clamp was applied to the vertebral artery and another clamp applied to the subclavian, hoping that some anastomotic circulation would be retarded. Another incision was then made longitudinally in the posterior triangle of the neck anterior to the trapezius muscle. The spinal accessory nerve was exposed and retracted from the wound. The sac was opened and a large clot, perhaps 500 cc., was evacuated. Two openings into this sac were found to come from the vertebral artery at the interval between the fourth and fifth processes of the cervical vertebrae. Four sutures of silk and three silver clips were placed on the vessel which stopped all the bleeding. The vertebral vein was probably included in these ligatures and clips. The vertebral artery was then ligated but not divided at the point where it was previously dissected near its origin from the subclavian artery. (Fig. 7) The wounds healed without difficulty. There was no recurrence of the bruit at the time of discharge four months later.

CASE 6.—*A-V fistula, left vertebral vessels, second portion, due to injury from falling log February 13, 1945. Removal of transverse process of second cervical vertebra. Multiple ligation of vessels and application of silver clips at point of fistula, May 24, 1945. Cured.*

On February 13, 1945, this soldier was struck on the left side of the face and neck by a falling log. There was no evidence of a penetrating wound. The patient was unconscious for about 30 minutes. There was marked swelling of the left side of the neck for ten days. Severe headaches of the left parietal region were present for two weeks, with stiffness of the neck and tenderness along the cervical vertebrae. Following the injury a roaring sensation developed in the left ear which was accentuated by each heart beat. About a month after injury the presence of a continuous bruit was noted in the upper posterior portion of the left neck inferior to the mastoid. On admission to the Ashford General Hospital, three months later, there was no evidence of an external wound, but a continuous bruit and thrill were present in the left side of the neck just below the mastoid. Occlusion of the common carotid artery did not cause the bruit to disappear. It was thought that this was an arteriovenous fistula of the second portion of the vertebral vessels.

On May 24, 1945, a longitudinal incision was made on the left side of the neck extending from the mastoid process to the level of the thyroid cartilage. The sternomastoid muscle was retracted laterally and the carotid vessels medially. The transverse processes of the first, second, and third cervical vertebrae were exposed by detaching the levator scapulae muscles from the transverse processes of the atlas and axis, and detaching the spinalis muscles from the transverse processes of the first, second, and third cervical vertebrae by sharp and blunt dissection. The fistula was apparently at the level of the inferior border of the vertebral canal of the second cervical vertebra. The roof of the foramen transversarium of the second cervical vertebra was removed by rongeur. This allowed exposure of approximately 2.5 cm. of the vertebral vessels. Ligatures of silk were passed about the vessels proximal and distal to the fistula and the vessels doubly ligated above and below the fistula. This caused the bruit to diminish but not disappear. The collateral vessels were ligated in a similar manner which caused the bruit and thrill to completely disappear. Silver clips were applied to the vessels proximal and distal to the fistula. The wound healed without difficulty. Although the patient developed Horner's syndrome following the operative procedure, there was no evidence of injury to the posterior root of the second cervical nerve. The bruit and thrill had not recurred at time of discharge three months later.

CASE 7.—*A-V fistula, right vertebral vessels, second portion, due to shell fragment wounds February 20, 1945. Quadruple ligation of vessels, July 27, 1945. Cured.*

On February 20, 1945, this soldier received high explosive shell fragment wounds of the right side of the neck, shoulder, arm, and chest wall. The wound of the neck bled profusely and was controlled by a pressure bandage. The right upper extremity was paralyzed at the time of injury but there was returning function at the time of admission to the Ashford General Hospital. The wounds of the neck were not débrided. Within 24 hours after admission to an Evacuation Hospital, the presence of a bruit and thrill were discovered in the right side of the neck. Examination at the time of admission to the Ashford General Hospital, June 11, 1945, revealed a small scar in the right lower neck. A definite thrill was felt and a continuous bruit heard in this region. The bruit was transmitted up the course of the carotid vessels and also along the axillary vessels. The bruit and thrill could not be completely obliterated by pressure. Almost complete obliteration caused the pulse to drop from 92 to 84 and the blood pressure to change from 110/70 to 110/80. There was partial brachial plexus paralysis with atrophy of the right hand and fingers, but function was returning. On July 27, 1945, a curved incision was made along the anterior border of the sternomastoid muscle and then laterally over the proximal half of the clavicle. The

medial half of the clavicle, including its articulation, was excised subperiosteally. The attachment of the sternomastoid muscle to the periosteum of the clavicle was divided. The internal carotid artery and internal jugular vein were identified and isolated. The vertebral artery was isolated and occlusion of this vessel caused the bruit and thrill to disappear. Dissection of the vertebral artery and vein was then carried out up to the point where the vessels entered the sixth cervical vertebra. The vessels in this region were involved in scar tissue and the fistula was found to be present at this point. The proximal artery was ligated and divided. Dissection was continued until the point of entrance into the transverse process was completely isolated. It was then planned to do a mass ligation of the artery and vein at this point. As this procedure was being carried out, the artery was torn at the site of the fistula. Bleeding was controlled by digital pressure and the roof of the foramen transversarium of the sixth cervical vertebra was removed by rongeur. The interspace between the fifth and sixth vertebra was then cleared, permitting visualization of this segment of the vessels. Silk ligatures were passed about the vertebral vessels and the vessels ligated. This completely controlled the bleeding. The proximal vein was then ligated and divided. There were no postoperative complications, and no recurrence of the bruit.

CASE 8.—*A-V fistula, left vertebral vessels, first portion, due to shell fragment wounds February 28, 1945. Excision of fistula with false sac, June 15, 1945. Cured.*

This soldier received mortar shell wounds of both legs, back, and left side of the neck, on February 28, 1945. There was no excessive bleeding. He was unable to talk for four or five days following injury, but his voice gradually returned to normal. During January 1945, two attempts were made to remove foreign bodies from the neck but both attempts were unsuccessful. During an eye examination in June 1945 the presence of a bruit and thrill in the left lower portion of the neck was discovered. On admission to the Ashford General Hospital, June 15, 1945, there was a definite Horner's syndrome on the left and a partial left facial palsy. There were three small scars on the left side of the neck and beneath the superior scar a thrill was palpable. On auscultation a continuous bruit was heard. The bruit and thrill could not be obliterated by pressure occlusion of the common carotid artery. The bruit was transmitted along the course of the left transverse cervical vessels which were thought to be the site of the lesion. On August 2, 1945, a transverse incision was made over the medial half of the left clavicle and the middle third of the clavicle resected subperiosteally. A longitudinal incision was made between the two heads of the sternomastoid muscle with the lower end of the incision forming an inverted "T" with the transverse incision. The two heads of the sternomastoid muscle were separated, the carotid sheath was opened and there was no evidence of the fistula involving the carotid artery and internal jugular vein. The transverse cervical and transverse scapular arteries were isolated as they crossed the anterior scalene muscle and these vessels were traced to their origin from the subclavian as the thyrocervical trunk. The fistula did not involve these vessels. The subclavian artery was isolated medial to the anterior scalene muscle. The vertebral artery was isolated at its origin and occlusion of this vessel caused the bruit and thrill to disappear. During the dissection of the vertebral artery, the vessel was torn at its origin and it was necessary to ligate the subclavian artery proximal and distal to the origin of the vertebral. The vertebral artery and vein were then dissected distally and a false sac, measuring about 2 cm. in diameter, was encountered with the distal portion of the sac lying near the foramen transversarium of the sixth cervical vertebra. The sac was opened during the dissection and hemorrhage controlled by digital pressure until silk ligatures were passed about the distal artery and vein. After ligation of these vessels and ligation of the proximal vein there was no further bleeding. The portion of vessels containing the fistula and the false sac was excised. The thoracic duct was ligated and divided during the dissection. There were no postoperative complications and no evidence of accumulation of chyle

in the wound. His convalescence was normal and there was no recurrence of the bruit.

CASE 9.—*A-V fistula, right vertebral vessels, second portion, due to shell fragment wounds, July, 1944. Removal of transverse processes of the second and third cervical vertebrae and mass ligation of fistula, December 8, 1945. Cured.*

This soldier was wounded in July, 1944, by fragments of a high explosive shell. There was a wound below and behind the right mastoid process and a wound on the back of the right hand. He was unconcious for fifteen minutes and bled profusely from the wound in the neck. The wounds were débrided and he was returned to England where the fragment was removed from the right hand. Forty-three days after injury he was returned to combat duty. Four months later he was evacuated because of combat exhaustion. Upon routine physical examination the presence of an aneurysm of the right neck was discovered and he was returned to the United States. On admission to the Ashford General Hospital, November 21, 1945, his only complaint was that of a buzzing sensation in his right ear when lying on that side. Examination on admission showed a healed wound just posterior to the upper third of the right sternomastoid muscle. In this region a thrill was felt and a continuous bruit heard. The bruit was transmitted throughout the neck, upward behind the ear. It was easily obliterated by pressure over the right common carotid artery. Upon obliteration of the fistula the pulse fell from 80 to 72 per minute and the blood pressure rose from 120/68 to 120/80. A diagnosis of arteriovenous fistula of the internal carotid artery and internal jugular vein was made. On December 8, 1945, an incision was made parallel to the anterior border of the right sternomastoid muscle. Since it was thought that the fistula involved the internal carotid artery, the carotid vessels were identified at their bifurcation and ligatures passed about the common, internal, and external carotid arteries. Occlusion of these vessels singly or in combination did not diminish the bruit. Compression at a slightly lower level in the neck obliterated the thrill. Dissection was carried out inferiorly and the vertebral artery was identified. It was found that occlusion of this vessel stopped the bruit and thrill. Ligatures were passed about the vertebral vessels. The incision was then extended upward with detachment of the sternomastoid, longus colli, splenis capitis and levator scapulae muscles from their origins. In this manner the transverse processes of the upper two cervical vertebrae were exposed. The transverse processes of the second cervical vertebra were removed and a ligature was passed about the vertebral vessels at this point. Occlusion of the vessels did not result in cessation of the thrill. The third transverse process was similarly removed with isolation of the vessels at the level of the third cervical vertebra. Compression at this point resulted in cessation of the thrill. The vertebral vessels were then ligated at the site of the second and third transverse processes. A mass ligature was tied in the interval between these sutures with further obliteration of a segment of vessel. Slight bleeding was encountered at this time due to the tearing of small branches of the vertebral artery. A tantalum clip was applied at the site of the fistula to further insure occlusion. The vertebral artery was doubly ligated in its first portion and a tantalum clip was applied at the point at which it entered the sixth vertebra. His recovery was normal. There was no recurrence of the bruit and the condition was considered as cured on discharge two months later.

CASE 10.—*A-V fistula, left vertebral vessels, third portion, due to shell fragment wound, December 18, 1944. Preliminary temporary occlusion of vertebral artery in the first portion, removal of transverse process of the atlas, and mass ligation of the fistula, January 31, 1946. Cured.*

This soldier was wounded in action December 18, 1944, when he was struck in the left side of the neck by a shell fragment. The wound of entrance was just inferior and posterior to the angle of the mandible. There was no wound of exit. There was no excessive bleeding and no loss of consciousness. The wound was

allowed to heal by second intention. There was marked diminution in the hearing of the left ear after the injury, and he was conscious of a continuous buzzing in that ear. He was evacuated to the United States and admitted to the Ashford General Hospital on November 8, 1945. Examination revealed a scar, about 1 cm. in diameter, just inferior and posterior to the angle of the left mandible. There was a small sinus in the region of this scar from which a small amount of serous fluid could be expressed. A continuous thrill was heard over this region, which was transmitted to the base of the neck. The bruit could not be obliterated by occlusion of the common carotid artery or by pressure anywhere in the neck. A diagnosis of vertebral arteriovenous fistula was made. On January 31, 1946, a 6-cm. transverse incision was made above the medial end of the left clavicle. The two heads of the sternomastoid muscle were separated and the vertebral artery, near its origin from the subclavian, was isolated. Occlusion of the artery caused the bruit to be diminished but did not completely obliterate it. This wound was covered, and a 10-cm. longitudinal incision was made along the medial edge of the sternomastoid muscle extending from the level of the thyroid cartilage upward to the mastoid process, and then curved laterally over the mastoid process so that the sternomastoid muscle was detached at its insertion. The spinal accessory nerve was isolated and the sternomastoid muscle reflected outward and downward. The splenius capitis muscle was reflected downward from the transverse process of the atlas which exposed the vertebral vessels between the axis and atlas. Compression of the vessels in this region caused the bruit to be diminished but not completely obliterated. It was then felt that the fistula involved the third portion of the vertebral vessel. The rectus capitis muscle was detached from its origin to the transverse processes of the atlas and axis and reflected downward which exposed approximately 2 cm. of the third portion of the vessels. It was necessary to remove the transverse process of the atlas in order to adequately expose the third portion of the vessels. The vessels were mass ligated distal and proximal to the fistula with two ligatures which were passed about the vessels. This caused the thrill to completely diappear but the bruit was still slightly audible. It was assumed that there were branches between the proximal and distal ligatures. Three other sutures were passed about the vessels between the proximal and distal ligatures which caused the bruit to completely disappear. The vessels were not divided. The divided muscles were approximated with interrupted silk sutures. The postoperative course was uneventful. There was no evidence of recurrence of the bruit or thrill two months after operation.

REFERENCES

[1] Matas, R.: Traumatisms and Traumatic Aneurysms of the Vertebral Artery and their Surgical Treatment: Report of a Cured Case. ANNALS OF SURGERY, **18,** 477, 1893.

[2] Perrig, H.: Zur Anatomie, Klinik und Therapie der Verletzgungen und Aneurysmen der Arteria Vertebralis. Beitr. z. klin. Chir., **154,** 272, 1932.

[3] Heifetz, Carl J.: Traumatic Aneurysm of the First Portion of the Left Vertebral Artery. Case Report. ANNALS OF SURGERY, **122,** 102, 1945.

[4] Henry, Arnold K.: Exposures of Long Bones and other Surgical Methods. Bristol: John Wright & Sons, Ltd., 1927.

DISCUSSION.—DR. RUDOLPH MATAS, New Orleans, La.: Doctors Elkin and Harris have presented a contribution of outstanding merit in the surgical history of the vertebral arteries. Their experience with the arteriovenous aneurysms of these arteries is unequalled in the number of cases reported. Their anatomic studies of the vertebrals from their origin in the subclavians and their long travel to the base of the brain, inside the osseous encasement of the vertebral canal, is in accord with the physiologic importance as feeders of the medulla, and with the need for their protection against injury and accident. It is by a study of these natural defenses, so well-presented by the authors, that the comparative rarity of wounds and aneurysms of

these vessels is explained. It is because of these defenses that their surgical attack was so long delayed. For it was as late as 1836 that Sanson, of the Paris Faculty, declared that the vertebral arteries were so hidden and inaccessible that "they were beyond the reach of surgery." And so it is that it was not until 1852 that a vertebral artery was first ligated, for a gunshot wound, in a memorable operation performed by Maisonneuve and Favrot.

And it is from the viewpoint of the anatomic approaches to the vertebrals and as a contrast between the old and the new in the technic and therapy of surgery that the contribution of Doctors Elkin and Harris is especially valuable. The importance of the anatomy of the vertebral arteries for the differential diagnosis of vertebral from the carotid and deep subclavian cannot be too strongly emphasized.

It was my fortune to encounter an aneurysm of the vertebral artery very early in my surgical career. The patient, a Negro boy, age 21, was brought to my service at the Charity Hospital in July, 1888. As the result of a bullet wound, a traumatic (arterial) aneurysm, complicated by a temporary hemiplegia, developed in the right suboccipital region which was clearly differentiated from a carotid (occipital branch) injury, when the common carotid was temporarily controlled. Despite all efforts to induce coagulation by icebags, direct compression and electrolysis, the tumor continued to enlarge and compelled an operation, two months after the injury, in fear of rupture of the sac. After due preparation, the tumor was incised freely and the bleeding quickly controlled after scooping out a pseudosac of organized clot, and packing the bleeding artery in the vertebral canal of the axis. Pieces of *aseptic sea sponge* (an essential part of our surgical equipment at that time) were used very effectively to pack the osseous canal and allowed to remain as a permanent plug. The rest of the cavity was packed with iodoform gauze which remained *in situ* for five days, after which the pack was removed and the wound allowed to close. The patient made an excellent recovery as the paralytic symptoms cleared spontaneously, and was allowed to return home on the 11th day. No search was made for the bullet and the marine sponge pack remained permanently incorporated in the tissues. As a result of this experience, I wrote a monograph on "Aneurysms and Wounds of the Vertebral Arteries,"* in which the history and casuistry of these injuries is fully summarized.

Confirming the clinical rarity of vertebral wounds and aneurysms, I found, in a statistical study of the Charity Hospital, that in a total of 463,894 admissions, from 1832 to 1892 inclusive, no case of vertebral aneurysm or injury had been admitted until the patient operated upon in my service in July, 1888. Another traumatic aneurysm of the vertebral artery, in a Negro slave, had been successfully operated upon in 1849, by Dr. Warren Stone in his private infirmary, by free incision and packing. These are the only two cases (both arterial) of wounded vertebrals recorded in New Orleans up to the time of my publication in 1893, and I know of no other cases in New Orleans since that time. It is also noteworthy that only two cases of bleeding wounds of the vertebrals are recorded in a list of 245,790 gunshot wounds and 1,922 saber and bayonet wounds, in the official history of the Civil War in the United States from 1860 to 1865. It is only in modern wars, especially the two world wars, that *arteriovenous aneurysms* of the vertebral arteries began to appear. Sir George Makins reported three vertebral (arterial) aneurysms (only one operated upon) in 1,911 hospitalized British war casualties, classified according to the individual arteries injured. Hermann Kuttner, of Breslau, in a notable essay which covered the German experience of World War I, up to 1918, was able to collect only seven war aneurysms of the vertebrals in the neck, of which two were arteriovenous. Bier, despite his great authority and experience, had only one case under his care, and von Haberer, with even greater experience, had none to report.

The preponderance of arteriovenous aneurysms in modern wars over the pure arterial, especially in World War II, is easily accounted for by the enormous increase

*Annals of Surgery, Vol. 18, 477, November, 1893.

in artillery fire in which showers of small, sharp flying fragments of exploding bombs, shells and hand grenades greatly increased the liability to penetration of the best protected vascular areas.

In accord with modern experience, the mortality of the vertebral wounds is always greater in patients operated upon in the field as emergencies than in those operated upon for aneurysms, especially for arteriovenous, after recovery from the primary injury. The fact that 53 wounds and aneurysms of the vertebrals were collected from the literature up to 1893 — all were arterial and none arteriovenous — is remarkable. Eliminating 11 endocranial aneurysms as essentially postmortem findings, we find that of 20 patients who survived long enough to develop aneurysms, only six recovered — a mortality of 70 per cent. Of 22 wounds and nonaneurysmal injuries only two recovered, leaving a mortality of 90 per cent!

The wounds were almost equally divided between those caused by punctures and stabs (79.16 per cent) and gunshot injuries (78.14 per cent). This is interesting in showing the difference in pathologic effects caused by a diversity of weapons and missiles used at different periods in the history of civilian strife and organized warfare. Two notable exceptions were fatal hemorrhages caused by erosion of the arteries in tuberculous abscesses of the vertebrae.

The essential causes of death were hemorrhages, shock, sepsis, associated complications, particularly brain disorders following erroneous ligations of the common carotid artery. Practically all the cases of aneurysms and wounds that recovered were treated by packing the wound and plugging the vertebral canal. In one case in which the vertebral artery was completely divided by a bullet, there was no hemorrhage, an exception due to complete retraction and retreat of the divided artery inside the vertebral canal.

While it is probable that many of the wounded in the high vertebral (suboccipital) regions are killed outright on the field of battle, it is evident from the report of Doctors Elkins and Harris that, apart from untoward complications, the chief factors in mortality have been virtually eliminated by modern practice in patients who have survived the effects of the primary injury.

While no attempt was made to make a special statistical study or record of vascular surgery in the United States history of World War I, the deficient records of vascular experience in that war have been more than compensated for by the magnificent contributions to surgical knowledge that have sprung out of the experience of the Army Vascular Centers so wisely organized by the Surgeon-General, of which the Ashford General Hospital at White Sulphur Springs, under the direction of Colonel Elkin, will remain a monumental example.

DR. WILDER PENFIELD, Montreal, Quebec: I would like to add to Doctor Elkin's approach one other method which we found necessary a few months ago in aneurysm of the vertebral artery. This was in a patient who had von Recklinghausen's disease. There was no bruit and we assumed there was an intraspinal neoplasm. However, I found at the level of the second cervical vertebra an arteriovenous aneurysm within the canal but outside the dura. I carried out laminectomy and ligated the vertebral artery below, between C–5 and C–6, making the approach posteriorly, and then packed the aneurysm with gelatin sponge, making an opening in the dura. It looked satisfactory when we stopped, but the patient was not relieved of pain in the neck and the paraplegia continued to advance. Therefore, we went in again, making a lateral cerebellar approach, and tied the vertebral artery near the pons, and had a completely satisfactory clinical result. I question whether the approach of Doctor Elkin would have been safe at that high level, even if we had been able to make the diagnosis beforehand.

STUDIES ON THE USE OF GELATIN SPONGE OR FOAM AS AN HEMOSTATIC AGENT IN EXPERIMENTAL LIVER RESECTIONS AND INJURIES TO LARGE VEINS*

HILGER PERRY JENKINS, M.D., AND RUDOLPH JANDA, 1ST LT., M.C., A.U.S.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, THE UNIVERSITY OF CHICAGO, SCHOOL OF MEDICINE, CHICAGO, ILL.

THE MAJOR CONTRIBUTIONS in the field of absorbable hemostatic agents which have been made by Ingraham and Bailey[1] on fibrin foam and by Frantz[2] on oxidized cellulose have been received with considerable interest by the surgical profession. An additional hemostatic agent, gelatin sponge, has recently been described by Correll and Wise,[3] and has since been the subject of papers by Pilcher and Meacham,[4] Light and Prentice,[5] and Correll, Prentice, and Wise.[6] The work of these authors has established this material as a valuable addition to the field of hemostatic substances.

Gelatin sponge has been of interest to us from the standpoint of the general surgeon and studies on its absorption[7] and hemostatic[8] action have been reported. The excellent hemostatic properties of gelatin sponge has led us to further studies of a more critical nature. A preliminary report on part of this work has been presented.[9]

In a series of 12 dogs, which were operated upon with aseptic technic, and under ether anesthesia, a considerable portion of a lobe of the liver was resected by simply cutting it off with scissors. The gelatin sponge was prepared for use by moistening in physiologic saline solution, expressing the air, and then removing the excess saline by compressing between dry gauze. No thrombin was added to the gelatin sponge in this series of animals. The large gelatin sponge was placed over the freely bleeding stump of liver so that it overlapped the upper and lower surface of the liver. (See Plate IA, showing hemorrhage from resection of portion of lobe of liver and its complete control by application of gelatin sponge.) The sponge was held in place with firm pressure for five to ten minutes. Care was taken to obtain good apposition of the sponge to the bleeding surface, as this produced a relatively rapid adhesive effect between the raw surface of the liver and the sponge.

Hemostasis was obtained in all of these animals by the application of the gelatin sponge alone, without any supplementary suturing. It was necessary, however, to reapply a fresh gelatin sponge in several instances to obtain complete hemostasis. All of these animals survived the immediate postoperative period. Two of the animals died at four and five days, respectively,

* This work was aided, in part, by a grant from the Upjohn Co. to the University of Chicago.

Read before The American Surgical Association, April 2–4, 1946, Hot Springs, Virginia.

from what appeared to be a bile peritonitis. The other animals were sacrificed at varying periods of time from two days to six weeks after the operation. There was no evidence of secondary hemorrhage from the liver in this series.

At autopsy, the gross appearance of the liver and the condition of the sponge varied according to the length of time after operation. (See Fig. 1A and B, showing photographs of specimens of liver and gelatin sponge at different lengths of time after operation.) Within the first four days the gelatin sponge was a red friable soggy mass which was quite firmly adherent to the liver stump. In attempting to remove it from the liver the sponge would usually fragment. Light fibrinous adhesions would usually be present between the sponge and the omentum or surrounding structures.

FIG. 1-A.—Showing specimen of liver at 8 days, with gelatin sponge covering raw surface.

After about a week the gelatin sponge became more firm and tough and sometimes had a glassy gelatinous appearance. Adhesions of varying magnitude would often be present but could usually be easily separated. After two weeks the gelatin sponge was usually covered by adhesions to omentum or surrounding organs which were difficult to separate without opening into the gelatin sponge mass which was well-encapsulated between the stump of liver and surrounding structures. After three weeks the gelatin sponge was usually buried in some adhesions which were often less than observed earlier. After four weeks or more the gelatin sponge was not easily identified and the stump of the liver was usually quite well healed over although often buried in some adhesions to surrounding structures.

The microscopic studies presented some rather interesting points. During the first few days there was a slight but not conspicuous leukocytic reaction to the sponge. After a week there was evidence of very active

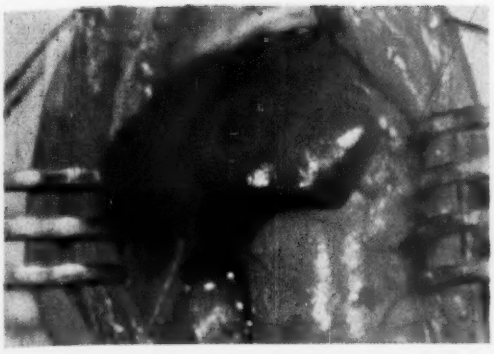
fibroplasia across the stump of liver under the cover of the gelatin sponge. (See Plate IIA, B, C and D, showing photomicrographs of the gelatin sponge covering the healing stump of liver at varying periods of time after operation.) This fibroplasia appeared to extend into the interstices of the sponge which were filled with red blood cells. There was beginning absorption of the sponge adjacent to this area of fibroplasia. After two weeks there was more mature fibroplasia which invaded the sponge to a greater extent and which has resulted in encapsulation of the sponge. There was evidence of some absorption along the entire periphery of the sponge although there was little change in the central portions of the sponge. After three weeks the fibroplasia has resulted in fairly well-differentiated connective tissue covering

FIG. 1-B.—Showing liver after 1 month with healing of stump of resected lobe and disappearance of the sponge surface.

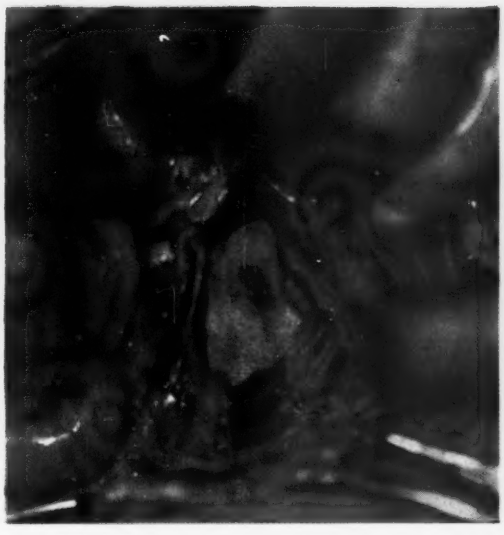
of the stump of the liver and there is evidence of more advanced absorption of the sponge and invasion of the interstices by macrophages. After a month or more there may be no evidence of gelatin sponge or there may be a well-encapsulated residuum which is in an advanced stage of absorption.

The second series of experiments on the hemostatic action of gelatin sponge consisted of producing wounds in large veins to determine whether such massive venous hemorrhage could be controlled. In a series of 36 dogs, which were operated upon with aseptic technic, and under ether anesthesia, the femoral, jugular, or renal veins or the vena cava were exposed. A stab incision was made with a scalpel or a portion of the wall of the vein was excised. The latter procedure was preferred as it gave a more massive hemorrhage. (See Fig. 2 and Plate I, showing hemorrhage from femoral vein and from vena cava which was controlled by application of gelatin sponge.) The gelatin sponge was applied immediately to the bleeding vein and pressed firmly in place over the wound for one to two minutes. It was found that pressure with the gloved finger directly on the sponge on the vein was more satis-

A



B



C

D

PLATE I

PLATE I.—A.—Showing hemorrhage from liver resection.

B.—Showing control of hemorrhage by application of gelatin sponge over bleeding stump of liver.

C.—Showing hemorrhage from vena cava (column of blood caught by camera before splashing back on wound).

D.—Showing control of bleeding by application of gelatin sponge.

factory than pressure transmitted through saline-soaked gauze which required subsequent removal and sometimes dislodgement of the gelatin sponge. Improvements in the technic of applying pressure will undoubtedly be worked out in subsequent studies. The bleeding was completely controlled in all experiments except two. These two failures were in the series of 22 experiments where the wound was made in the abdominal portion of the inferior vena cava. Of the four experiments where the wound was made in the thoracic portion of the inferior vena cava and the two experiments on the superior vena cava there was one secondary hemorrhage from the latter. This was apparently due to the motion of the lungs which dislodged the sponge after the chest wound was closed. In the experiments on the abdominal vena

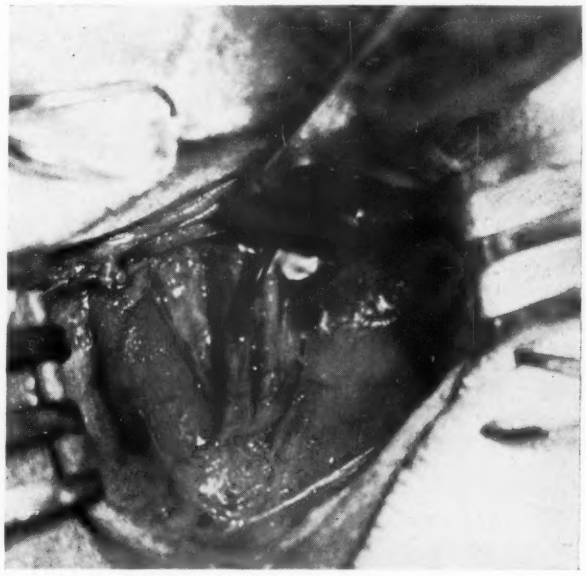


FIG. 2-A.—Showing hemorrhage from femoral vein of dog.

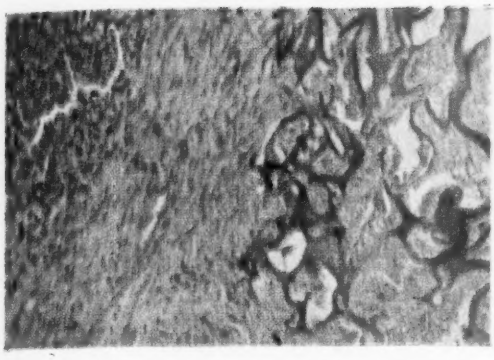
cava a layer of peritoneum was closed over the sponge which thus apparently prevented subsequent dislodgment in this series.

The animals were sacrificed at varying periods of time from 12 hours to 60 days after operation. Within 12 hours the gelatin sponge was firmly adherent to the wall of the vein. (See Fig. 3, showing vena cava.) The defect in the wall of the vein could be readily identified up to five days, or more, with the gelatin sponge forming a well-sealed patch over the defect. After six to eight days there was often a thin transparent membrane covering the gelatin sponge which was plugging the rent in the vein. After eight to twelve days the wound in the vein usually appeared to be closing over. After three weeks there was evidence of an endothelized scar. In some instances where a small incision was made in the vein instead of removing a small segment of the wall of the vein it was difficult to identify the point where the wound had been made after two weeks or more. In two of the experiments where the animal

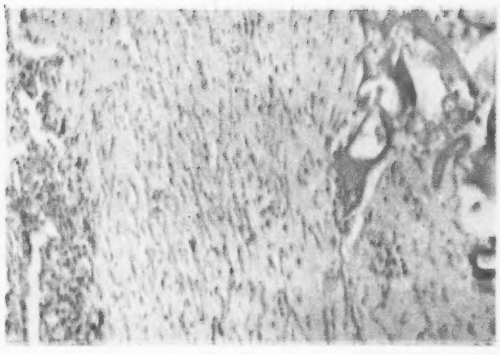
FIG. 2-B.—Showing control of hemorrhage from femoral vein by application of gelatin sponge "patch."

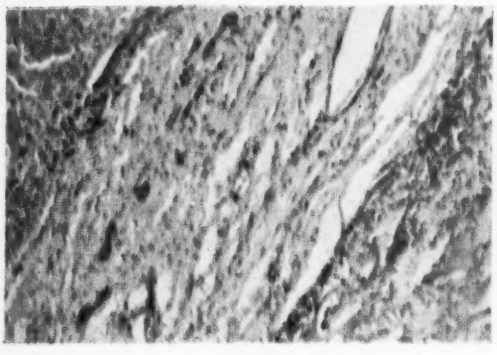
FIG. 2-C.—Showing hemorrhage from vena cava of dog.

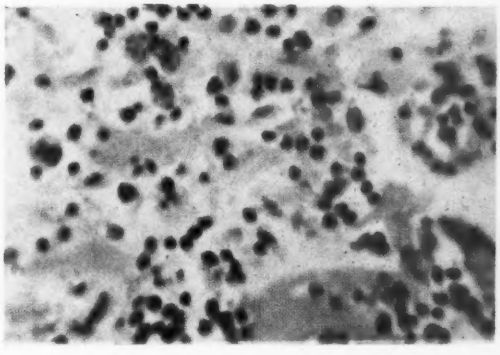
A



B







C

D

PLATE II

PLATE II.—A.—Showing photomicrograph of healing stump of liver, with active fibroplasia at 8 days, covered by gelatin sponge which is being invaded by fibroblasts.

B.—Showing photomicrograph of liver at 2 weeks, with more advanced fibroplasia over liver stump and invasion of sponge which forms protective cover over this reparative process.

C.—Showing photomicrograph of liver at 3 weeks, with evidence of more advanced differentiation of the connective tissue, and invasion of the sponge with macrophages, mononuclears, and leukocytes. There is also connective tissue deposited in the sponge interstices and moderate degree of absorption of the sponge.

D.—Showing advanced absorption of sponge after one month. A few spicules of the sponge can be seen, there is invasion by macrophages, lymphocytes, and some polymorphonuclear leukocytes.

was sacrificed within a few days there was a small clot adherent to the sponge plugging the wound of the vein. In another instance there was an organized thrombus adherent to the vein wall where the wound had been produced sixteen days previously. This did not produce occlusion of the vessel. In one animal there was moderate constriction of the lumen of the vein where a large oval shaped segment of vein wall was removed twenty-six days previously and the defect covered with a gelatin sponge patch. In several other experiments where a moderate sized piece of vein wall was removed there was no apparent constriction. The gelatin sponge could usually be readily identified during the first week. After one to two weeks the sponge became surrounded by a capsule of fibrous tissue. After a month it was usually difficult to identify the gelatin sponge grossly.

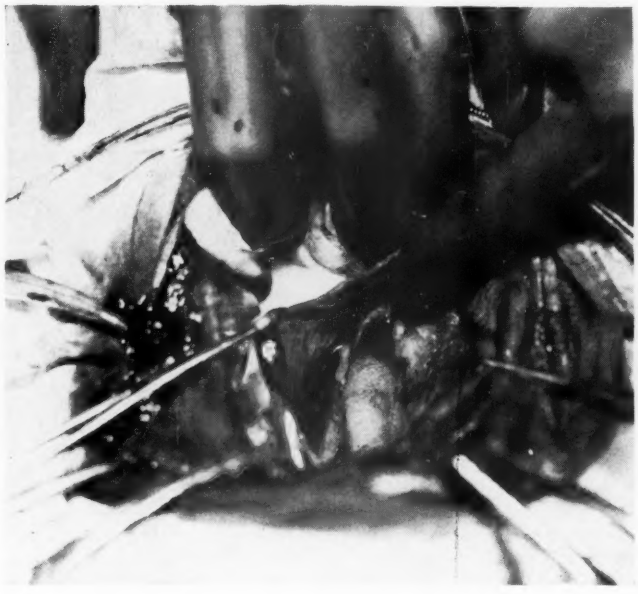


FIG. 2-D.—Showing control of hemorrhage from vena cava by gelatin sponge "patch" three minutes after application.

In addition to these experimental studies, we have used gelatin sponge on 76 patients. Satisfactory hemostasis has been obtained with the sponge in a variety of surgical procedures where troublesome bleeding could not be completely controlled by other means. The magnitude of the bleeding which occurred in these procedures was rarely comparable to that which was obtained in the series of experimental procedures and, therefore, our clinical tests do not represent as critical an evaluation of the hemostatic properties of the gelatin sponge as our experimental tests.

COMMENT: In our observations on gelatin sponge it would appear that a substantial part of the hemostatic action may be due to the spongy material itself. It is possible that the enormous surface-area of the myriads of interstices may attract and damage the platelets in the blood which enters the

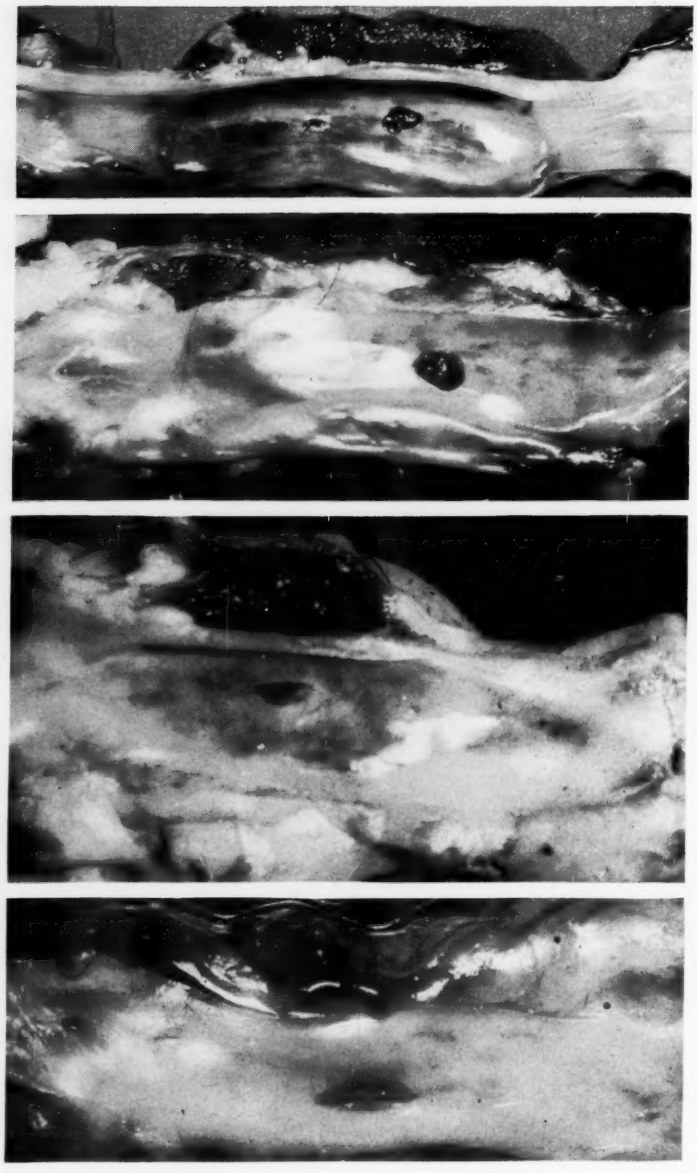


FIG. 3-A.—Showing specimen of vena cava 12 hours after application of gelatin sponge "patch" which firmly seals off a large and a small wound in the wall of the vessel.

B.—Showing vena cava four days after gelatin sponge "patch" for wound in wall of vessel.

C.—Showing vena cava 8 days after gelatin sponge "patch." The sponge has become encapsulated on the tissues surrounding the vein, and the defect in the wall of the vein is closing over.

D.—Showing vena cava 28 days after "patch." There was a fairly large wound which has healed over leaving an endothelized scar.

sponge, thus, liberating thromboplastin. This in combination with the calcium and prothrombin in the blood may elaborate enough thrombin to initiate the clotting mechanism. The addition of prepared thrombin undoubtedly enhances and accelerates the hemostatic action of gelatin sponge, but we are not prepared to estimate the extent to which it does so. In the clinical use of gelatin sponge it is, therefore, recommended that thrombin be used to obtain the maximum hemostatic effect.

Our observations on the use of gelatin sponge in controlling bleeding in experimental liver resections and in clinical biopsies would suggest the possibility of using this material to control bleeding as a result of resection of tumors of the liver in patients. We are not as yet prepared to make this recommendation until further details in the technic of applying the sponge have been worked out. Furthermore, it would be desirable to have a somewhat stronger and tougher spongy material than is now available. This would make it possible to suture the sponge to the upper and lower surface of the liver by some sort of basting-stitch to securely hold it in place. Although the absorption time of the sponge which we have used may be more than adequate under favorable conditions it must not be overlooked that the sponge may become rapidly liquefied in the presence of a considerable concentration of leukocytes. This may account for the two cases of bile peritonitis in our experimental series, as the rapid liquefaction of the sponge would remove any barrier to the outpouring of bile from the intrahepatic ducts which otherwise remained sealed-off by the gelatin sponge until healing occurs.

The excellent protective cover which the sponge appears to offer to the healing process across the stump of liver at the line of resection is of considerable interest as is also the structural support it seems to give the reparative process. This is a rather fundamental point which deserves further study as it is quite unusual for any foreign material to aid the normal process of repair.

The principle of utilizing a patch of hemostatic material to control bleeding from large dural sinuses has been practically a standard technic among neurosurgeons since the introduction of muscle patches or stamps by Cushing in 1911.[10] As a result of the work of Ingraham and Bailey, fibrin foam has largely replaced the muscle-patch technic in the past few years. Recently, Pilcher and Meacham, and Light and Prentice, have demonstrated that gelatin sponge can be utilized as effectively as fibrin foam for this patch technic in controlling bleeding from the dural sinuses.

Our observations on the gelatin sponge-patch technic for controlling massive bleeding from the large veins of the dog have not been carried on over a sufficient period of time or in sufficient number to as yet justify a recommendation on its clinical use by the general surgeon. A number of situations naturally suggest themselves where this technic would be of value.

In resections of the pancreas the superior mesenteric or portal vein may be injured in the course of dissecting away adherent tissue. This would be an especially suitable place for the application of gelatin sponge to pre-

serve the continuity of this vessel which one would not choose to ligate if there was any other alternative. In radical dissections of the neck or axilla one may find occasion to utilize such a patch technic if the jugular or axillary veins were opened during the course of the operation. Occasionally during thyroidectomy one may tear a lateral thyroid vein in mobilizing a large gland. If one is unable to get exposure of the bleeding vessel due to the large overlying gland the gelatin sponge would probably offer an alternative of value. There are innumerable conditions other than these where an absorbable hemostatic agent might prove helpful if not life-saving.

Wherever one can easily suture a rent in a major vein it is of course the procedure of choice and should take precedence over the application of an absorbable hemostatic patch. However, there may be value even here in utilizing gelatin sponge as a reinforcement to the suture line in the blood vessel.

The possibility of a propagating thrombus arising from the sponge plugging the rent in a vein must be considered as a possibility in the clinical application of this study. The use of heparin and dicoumarol therapy after operation may be required to prevent this eventuality. On the other hand, the experience of neurosurgeons with the patch technic, using muscle, fibrin foam, or gelatin sponge, on the dural sinuses has generally been quite good as they do not have a problem of subsequent thrombosis of these veins.

CONCLUSIONS

In view of our experimental observations in which we have been able to control extensive venous hemorrhage from liver resections as well as from direct injury of large veins, including the vena cava, it would appear that gelatin sponge has excellent hemostatic properties. An absorbable substance with these properties should find many uses in the hands of the general surgeon. There are, as yet, a number of points which should be worked out in the technic of handling this material to obtain the best results. In addition, it would appear that there may be a place for a spongy material with different degrees of absorbability as well as tougher and stronger physical properties which would lend itself to special uses. The particular promise which these hemostatic substances have to offer is that it may enable one to undertake more extensive surgery with greater safety, especially in the treatment of carcinoma, than has been feasible in the past.

REFERENCES

[1] Ingraham, F. D., and Bailey, O. T.: Clinical Use of Products of Human Plasma Fractionation. Jour. Am. Med. Assn., **126**, 680, 1944.

Idem: The Use of Products Prepared from Human Fibrinogen and Human Thrombin in Neurosurgery. Jour. Neurosurg., **1**, 23, 1944.

Idem: Studies on Fibrin Foam as a Hemostatic Agent in Neurosurgery: With Special Reference to its Comparison with Muscle. Jour. Neurosurg., **1**, 171, 1944.

Bailey, O. T., and Ingraham, F. D.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: XXI. The Use of Fibrin Foam as a Hemostatic Agent: Clinical and Pathological Studies. Jour. Clin. Invest., **23**, 591, 1944.

Bailey, O. T., Ingraham, F. D., Swenson, O., Lowrey, J. J., Bering, E. A.: Human Fibrin Foam with Thrombin as Hemostatic Agent in General Surgery. Surgery, **18**, 347, September, 1945.

[2] Frantz, V. K.: Absorbable Cotton, Paper, and Gauze (Oxidized Cellulose) **118**: 116, 1943.

Frantz, V. K., Clarke, H. T., and Lattes, R.: Hemostasis with Absorbable Gauze (Oxidized Cellulose). ANNALS OF SURGERY, **120**, 181, 1944.

Frantz, V. K.: New Methods of Hemostasis. Surg. Clin. North Am., **25**, 338, April, 1945.

Frantz, V. K., and Lattes, R.: Oxidized Cellulose—Absorbable Gauze. Jour. Am. Med. Assn., **129**, 798, November, 1945.

Lattes, R., and Frantz, V. K.: Absorbable Sponge Tests. ANNALS OF SURGERY, **121**, 894, June, 1945.

[3] Correll, J. T., and Wise, E. C.: Certain Properties of a New Physiologically Absorbable Sponge. Proc. Soc. Exp. Biol. & Med., **58**, 233, 1945.

[4] Pilcher, C., and Meacham, W. F.: Absorbable Gelatin Sponge and Thrombin for Hemostasis in Neurosurgery: Experimental and Clinical Observations. Surg. Gynec. & Obst., **8**, 365, October, 1945.

[5] Light, R. U., and Prentice, H. R.: Gelatin Sponge: Surgical Investigation of a New Matrix Used in Conjunction with Thrombin in Hemostasis. Arch. Surg., **51**, 69, September, 1945. *Idem:* Surgical Investigation of a New Absorbable Sponge Derived from Gelatin for Use in Hemostasis. Jour. Neurosurg., **2**, 516, 1945.

Light, R. U.: Hemostasis in Neurosurgery. Jour. Neurosurg., **2**, 414, 1945.

[6] Correll, J. T., Prentice, H. R., and Wise, E. C.: Biologic Investigation of a New Absorbable Sponge. Surg. Gynec. & Obst., **81**, 585, November, 1945.

[7] Jenkins, H. P., and Clarke, J. S.: Gelatin Sponge: A New Hemostatic Substance: Studies on Absorbability. Arch. Surg., **51**, 253, November-December, 1945.

[8] Jenkins, H. P., Janda, R., and Clarke, J. S.: Clinical and Experimental Observations on the Use of Gelatin Sponge or Foam. Surg., **20**: 124, 1946.

[9] Janda, R.: Observations on the Use of Gelatin Sponge. Surg., **20**: 299, 1946.

[10] Cushing, H.: The Control of Bleeding in Operations for Brain Tumor. ANNALS OF SURGERY, **54**, 1, 1911.

Note: The authors wish to express their appreciation to Dr. Eleanor Humphreys of the Dept. of Pathology of the University of Chicago and to Dr. Ormand Julian of the Dept. of Surgery of the University of Illinois College of Medicine and the Chicago Memorial Hospital for their participation in some phases of this work, and also to Dr. Edward Senz and Dr. Howard Owen.

DISCUSSION.—DR. WILLIAM JASON MIXTER, Boston, Mass.: I would just like to say that we who are doing neurosurgery can corroborate what has already been said, and I believe this will be a definite advance in general surgery as well as surgery of the brain. In surgery of the spinal cord there is one point of interest. I have been able to inspect three different specimens of gelatin foam in patients who were subjected to second laminectomies later. There seemed to be a smoother cleavage between the gelatin foam and the dura than there has been in the past where muscle was used to control bleeding from the dural veins. I think it is a definite step in advance. Fibrin foam works in the same manner.

DR. HILGER P. JENKINS, Chicago, Ill. (closing): I had planned to pay tribute in this presentation to Dr. Harvey Cushing for his introduction of the muscle "patch" which has been part of the standard technic of the neurosurgeon until the advent of the fibrin foam and subsequently the gelatin sponge. (This is covered in the manuscript but not mentioned because of the time limitation.) It behooves the general surgeon to take note of the technic of the neurosurgeon in controlling hemorrhage from veins by the "patch" technic, especially where one would not wish to sacrifice the vein by ligation or where ligature or vein suture may not be feasible.

PENICILLIN IN THE TREATMENT OF ESTABLISHED SURGICAL INFECTIONS*

A SYSTEMATIC STUDY OF 744 INCLUDING 82 SEPTICEMIAS

FRANK L. MELENEY, M.D.
NEW YORK, N. Y.

IN THE FALL OF 1943 when penicillin became available for clinical study, the Committee on Chemotherapy of the National Research Council assigned a limited quantity to several of the units which had been studying the prevention of infection in civilian accidental wounds and burns under the direction of the Subcommittee on Surgical Infections. These units then undertook to observe the effect of penicillin in the treatment of established surgical infections. These cases were reported to Doctor Keefer and they have been included in the all-inclusive reports which he has made from time to time, but the Subcommittee on Surgical Infections believed that it would be profitable to study the surgical cases separately, going into the details of the cases and recording in a systematic manner the circumstances of each case with the hope that a review and analysis of a fairly large number, might determine what circumstances contributed toward and what circumstances interfered with, a favorable outcome. It was thought that this might logically lead to methods of treatment which would improve the results by increasing the favorable circumstances and eliminating the unfavorable factors.

With the advice and council of Drs. Lowell Reed and John Fertig, Chairman and member, respectively, of the Subcommittee on Biostatistics of the National Research Council, the Subcommittee on Surgical Infections devised a summary sheet on which the items were listed which, it was thought, might play an important rôle in determining the outcome of the treatment. A copy of the summary sheet is enclosed with this report. The chief items have to do with the diagnosis of the surgical infection, its duration and its seriousness before instituting penicillin treatment, the nature of the previous surgical and drug therapy, the dosage and duration of penicillin and the method of its administration, the nature of associated medical or surgical treatments, the clinical symptoms and signs of infection and their persistence or disappearance, and the bacteriologic analyses before and after penicillin treatment. Finally, a well-considered judgment regarding the value of penicillin, in view of the previously noted factors, was recorded in each individual case.

The Committee recognized that there is often a great deal of difficulty in estimating the rôle played by any drug when it is used in conjunction with a surgical procedure, for a condition which in times past may have

* Work done under contract with the Office of Scientific Research and Development.
Read before the American Surgical Association, April 2–4, 1946, Hot Springs, Virginia.

responded satisfactorily to the surgical procedure alone. Surgical infections differ from medical infections in certain fundamental respects which make them less likely to respond to drug treatment. These differences have been described in detail in a number of recent publications but they may be profitably enumerated here because they must be considered in the appraisal of penicillin or of any other drug. Surgical infections are characterized by (1) a local spontaneous or traumatic breakdown of tissue or a localized exudation of leukocytes either into a body cavity, such as a joint or the pleura, or into the substance of solid tissues or organs, such as muscle or liver. This broken down tissue or cellular exudation must either be evacuated or absorbed before health is restored. (2) The blood vessels in the wall of an abscess are thrombosed and any medication coming *via* the blood stream may have difficulty penetrating or diffusing into the focus far enough to reach the offending organisms. (3) At the same time, in a well-localized lesion, the opportunity is afforded for the local application of the drug in question. (4) The bacterial species in surgical infections are often multiple and there may be a synergistic action between them. One or more of the species in any given infection may be either resistant to the bacteriostatic action of the drug or antagonistic to it. (5) When surgical infections are under control there is always the necessity for removal of the débris and repair of the tissue which may require more nutritive elements than are needed for the recovery from a medical infection. (6) Spontaneous surgical infections in contradistinction to those following injury are in the very beginning, before there has been any breakdown of tissue, similar to medical infections, in other words, there is a diffuse inflammation which may be called a cellulitis. Some surgical infections remain in the stage of cellulitis for several days and the tissue breakdown is slow. In others it is rapid. If drugs can be given before there is a breakdown of tissue it is reasonable to believe that they do not meet with the difficulties mentioned above but have a more favorable opportunity to contact and control any susceptible organisms.

The Subcommittee also realized that the complexity of a surgical infection made it almost impossible to run concurrently, a series of controls without any drug treatment or with some other form of drug treatment, the number of factors in any given case being so great, the time factor alone (duration of the infection before treatment) being infinitely variable. Surgical infections may be acute or chronic and there is no sharp line between them. The committee arbitrarily chose 30 days as the dividing line. Among the chronic cases there are those which go on for months or years without much change and those with acute exacerbation so that they must be classified as both acute and chronic. This is particularly true in cases of osteomyelitis. During the course of any chronic infection there may have been any number of operations as well as numerous local and general forms of medication — no two cases being alike. It is, therefore, impossible to obtain for study two parallel series, either by a process of alternating all cases or

by selecting two similar cases and assigning one to the treated series and the other to the control series.

In such circumstances the Subcommittee felt that it would be necessary to let certain chronic and subacute cases, in their previous course, be their own controls. In other cases it would be necessary to show some results in the drug-treated patients not seen in previous surgical experience when the drug under study was not available. For example, when an infection remains for days or weeks or months *in statu quo* or goes progressively down hill and then shows an abrupt improvement following the administration of a drug, it is reasonable to believe that the drug was responsible for the change. If this happens, not once, but many times it becomes more and more convincing. In the category of results not previously seen, we may list: (1) Those cases of surgical infection, formerly always requiring a surgical procedure, in which that procedure was completely obviated. (2) Those cases in which a limited surgical procedure with the aid of drug sufficed to effect a cure when formerly, without drug, a radical procedure would have been necessary. (3) Those cases requiring a surgical procedure but in which the healing time was definitely shortened by the use of drug. (4) Those cases permitting primary closure after incision or excision concurrently with the administration of drug and (5) those cases permitting an earlier successful secondary closure with drug than could have been obtained without drug.

In any group of surgeons there might be a difference of opinion regarding the classification of cases in any of these five categories. For example, in a case of cellulitis one might say that surgery was obviated, while another might say that he had seen similar cases which subsided spontaneously. Probably there would be more unanimity of opinion with reference to a condition such as acute suppurative arthritis which formerly almost invariably required incision and drainage to effect a cure and a return to normal function. There might be the greatest difference of opinion about cases in the third category, that of the shortening of healing time because no one can tell how long any given case will take to recover. One can estimate the healing time of a carbuncle following incision or excision but in both drug-treated and non drug-treated carbuncles there must be a separation of the tissue already destroyed when treatment began. This tends to equalize the healing time for cases in the two groups. The value of the drug treatment can sometimes be more clearly indicated by the disappearance of the causative organisms from the culture during the course of therapy, for in non drug-treated cases the cultures are almost invariably positive until the wound is healed.

Primary closure of a wound which has been made for the drainage of a purulent exudate was rarely successful before the advent of drugs. If that can now be done repeatedly with the aid of a drug, we may be fairly certain of the drug's efficiency. Secondary closure was not infrequently successful in World War I after a wound had been cleared of its slough and had been covered with healthy granulations. If with the aid of drug now there can be a strikingly higher percentage of successful wound healing or if sec-

ondary closure can be done earlier than formerly, the drug must be given credit for its share in the successful result. This is probably the most difficult criterion to weigh and measure accurately, in any particular case.

Bearing all of these things in mind, it is obvious that it may be difficult to appraise the value of a drug in any given case. However the Subcommittee felt that some approach to a satisfactory estimate could be made with regard to penicillin if the results could be classified as follows:

1. *Excellent* in cases responding abruptly or definitely within the first 72 hours after treatment began.
2. *Good* in cases clearly showing the benefit of the drug but over a longer period of time, perhaps a week or ten days.
3. *Questionable* in cases which might have done just as well without the drug as a result of the surgical procedure or some other associated treatment.
4. *No effect* in cases in which the infection was not altered in any way but ran its usual course.

These criteria were followed in the cases herewith presented. The largest single group of cases were observed by the author, and his associates, Dr. Harold Harvey and Dr. Robert H. E. Elliott at the Presbyterian Hospital in New York City. The next largest group were studied at the Pennsylvania University Hospital in Philadelphia by Dr. John Lockwood, Dr. Jonathan Rhoads and Dr. William White. The third largest group was cared for by Dr. William Altemeier at the Cincinnati General Hospital. The rest of the cases in smaller groups were treated in Detroit Receiving Hospital by Dr. John Hirshfeld, and his associates, at the Henry Ford Hospital by Drs. McClure and Lam and at the Charity Hospital by Drs. Ochsner and Caldwell, and their staffs. It has not seemed profitable to divide the cases into groups according to the units studying the problem. It may be assumed that they were treated in a similar manner and the summary sheets make certain that the factors associated with the case were recorded in a uniform manner. These data have been transferred to the McBee System punch cards for the purpose of analysis and the results of the study are given below.

There were approximately 1,000 cases of established surgical infections treated in all of the units put together. Approximately one-quarter of these cases were treated with various forms of sulfonamide or with zinc peroxide or some other antibacterial agent, but the treatment was too diversified to warrant analysis. This presentation will be limited to the cases which were treated with penicillin of which there were 744 with data sufficiently complete to yield a satisfactory analysis. These cover a wide variety of surgical diagnoses.

The accompanying tables give a list of the surgical lesions represented by five or more cases. The results are given in percentages in the four categories of "Excellent," "Good," "Questionable," and "No Effect." The first two may be considered favorable and the last two unfavorable. In the

Questionable group there may be cases in which the penicillin played a favorable rôle but it was not apparent to the observers and so we cannot score them to the credit of the drug.

It will be seen in Table I, giving the results for the series as a whole, that penicillin is of benefit in surgical infections and yet it is not a panacea. In about 15 per cent of the cases the response could be called dramatic or excellent, in 50 per cent definite or good, in 18 per cent doubtful or questionable, while in 18 per cent no effect could be demonstrated. It is necessary to study the cases carefully from many angles to determine what the conditions are for its success and why it often fails.

When the cases are divided into diagnostic groups it is seen that the results in some are very good, in others, intermediate and in others, poor.

TABLE I

SHOWING THE OVER-ALL RESULTS OF PENICILLIN TREATMENT IN SURGICAL INFECTIONS

	Results in Percentage					
	Favorable			Unfavorable		
Total Number of Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
744	14.8	49.9	64.7	17.8	17.6	35.4

TABLE Ia

SHOWING THE MOST FAVORABLE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Furuncle	26	53.9	38.4	92.3	7.7	0	7.7
Cellulitis	36	64.0	27.7	91.7	8.3	0	8.3
Mastoiditis	6	0	83.3	83.3	0	16.7	16.7
Carbuncle	28	39.3	42.9	82.2	14.3	3.6	17.9
Suppurative arthritis	22	18.2	63.5	81.8	4.5	13.6	18.1
Lung abscess	11	0	81.7	81.7	0	18.3	18.3
Superficial abscess	32	25.0	56.3	81.3	6.3	12.5	18.8
Brain abscess	5	0	80.0	80.0	0	20.0	20.0
Osteomyelitis	153	8.5	68.0	76.5	13.7	9.8	23.5

These are shown in Tables Ia, and Ib and Ic. Table Ia indicates that the best scores in the favorable columns were obtained by furuncles, cellulitis, mastoiditis, carbuncles, suppurative arthritis, lung abscess, superficial abscess, brain abscess and osteomyelitis, in that order, all of these lesions responding favorably in more than 75 per cent of the cases. The most brilliant results were obtained in the cases with cellulitis or furuncles and it is of interest that these two diagnoses are the only ones with zero in the "no effect" column.

The intermediate group shown in Table Ib includes deep abscess, thrombophlebitis, sinusitis, infected soft-part wounds, infected operative wounds, otitis media, infected compound fracture and ulcers of the skin. Favorable results were obtained in from 50 per cent to 75 per cent of these cases.

The poorest results, revealed in Table Ic, were obtained in empyema, burns, gas gangrene, actinomycosis, gangrene of the skin, miscellaneous surgical infections, postoperative pneumonia, peritoneal abscess, and, worst of all, diffuse peritonitis.

TABLE Ib

SHOWING THE INTERMEDIATE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Deep abscess	58	15.5	53.4	68.9	22.4	8.6	31.0
Thrombophlebitis	12	8.3	58.4	66.7	16.7	16.7	33.3
Sinusitis	6	0	66.7	66.7	0	33.3	33.3
Infected soft-part wound	37	13.5	51.3	64.8	21.6	13.5	35.1
Infected operative wound	70	5.7	55.6	61.3	21.4	17.2	38.6
Otitis media	7	28.6	28.6	57.2	14.3	28.6	42.9
Infected compound fracture	9	0	55.6	55.6	11.1	33.3	44.4
Ulcer of the skin	22	0	50.0	50.0	18.2	31.6	50.0

TABLE Ic

SHOWING THE LEAST FAVORABLE RESULTS OF PENICILLIN TREATMENT ACCORDING TO DIAGNOSIS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Empyema	34	0	47.0	47.0	26.5	26.5	53.0
Infected burn	31	3.2	42.0	45.2	29.0	25.8	54.8
Gas gangrene	9	11.1	33.3	44.4	33.3	22.2	55.5
Actinomycosis	7	0	42.9	42.9	28.6	28.6	57.2
Gangrene of skin	10	10.0	30.0	40.0	50.0	10.0	60.0
Miscellaneous	66	13.6	25.8	39.4	16.7	43.9	60.6
Postop. pneumonia	18	11.1	27.8	38.9	38.9	22.2	61.1
Peritoneal abscess	11	9.1	27.3	36.4	45.5	18.2	63.7
Diffuse peritonitis	18	5.5	22.2	27.7	22.2	50.0	72.2

All of these groups must be broken down in order to determine if possible why some cases succeeded and some failed, but first it would seem profitable to present the other factors which may play a rôle in the favorable outcome. It is generally believed that penicillin is more effective in acute than in chronic infections. Our cases may be divided into acute, chronic, with acute exacerbation, and chronic, without flare-up. The results are shown in Table II and they bear out the general impression but the difference is not as great as one would suppose. The chief difference is not in the combined figures for favorable results but in the figures for a prompt response in the "excellent" column. This clearly indicates that a larger pro-

portion of the acute cases respond dramatically to penicillin. Furthermore, the chronic cases with an acute exacerbation seem to give better results than those which smolder along without much change. However, other factors come into play in these two groups (particularly the nature and time of a surgical procedure) so that the over-all figure should not be given too great weight because these groups are not really comparable.

TABLE II

SHOWING THE RESULTS ACCORDING TO THE ACUTENESS OF THE PROCESS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Acute	477	20.1	46.6	66.7	17.4	16.0	33.4
Chronic, with acute flare	49	8.2	63.3	71.5	14.3	14.3	28.6
Chronic, without acute flare	218	4.6	54.1	58.7	19.3	22.0	41.3

TABLE III

SHOWING THE RESULTS IN THE ACUTE CASES ACCORDING TO THE DURATION OF SYMPTOMS BEFORE INITIATING TREATMENT

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Four days or less	145	26.9	43.4	70.3	14.5	15.2	29.7
Five days or more	319	17.9	47.6	65.5	19.1	15.4	34.5

In the acute cases the duration of the infection before the initiation of treatment bears an important relationship to the favorable outcome as is shown in Table III. In the chronic cases other factors are of more importance.

Of these cases, 662 were considered serious infections and 82 trivial. Favorable results were obtained in 64.9 per cent of the serious and in 88.6 per cent of the trivial cases. Of 384 cases which had received some form of sulfonamide prior to penicillin treatment, 65.4 per cent showed a favorable response. One would have expected that the cases which had failed to respond to the sulfonamides or to other drugs would have responded less readily to penicillin but such is not the case. It is of interest that such a large number failed to respond to the sulfonamides. However, we have no indication that during that treatment they developed any increased resistance to penicillin. This is shown in Table IV.

In 393 cases the lesion was closed, and in 351 it was open when treatment began. Favorable results were obtained in 67.4 per cent of the former and in 61.5 per cent of the latter, not a significant difference.

The relationship between penicillin and surgery in the treatment of these cases is revealed in Table V. It may be surprising to note that so many

cases (258) had no primary surgical procedure while under treatment in this study. Some of these were chronic infections and in the others, surgery was obviated by the use of the drug. In this first group, it is seen that there is a high incidence of excellent results and a sum total of favorable results somewhat better than the average. In the second group penicillin was tried first but did not suffice to control the infection and an operation was later resorted to. The results of the penicillin therapy were considered poor but this is a small group and, therefore, of less significance than the others. In the third group surgery was performed at the same time that

TABLE IV

SHOWING THE RESULTS OF PENICILLIN IN RELATIONSHIP TO PREVIOUS FORMS OF TREATMENT OF SURGICAL INFECTION

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
No previous treatment	259	20.1	44.8	64.9	17.8	17.4	35.2
Sulfonamides only	338	11.8	54.7	66.5	15.7	17.8	32.5
Other drugs only	39	25.6	41.0	66.6	20.5	12.8	33.3
Sulf. and other drugs	46	13.0	43.5	56.5	19.6	23.9	43.5

TABLE V

SHOWING THE RESULTS IN THE CASES WITHOUT SURGERY AND WHEN PENICILLIN PRECEDED, ACCOMPANIED, OR FOLLOWED AFTER A SURGICAL PROCEDURE

		Results in Percentage					
		Favorable			Unfavorable		
Time Relationship of Penicillin Administration to the Surgical Procedure	Total Number of Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
No surgery	258	22.8	43.8	66.6	14.7	18.6	33.3
Pen. before surgery	33	9.1	30.3	39.4	21.2	39.4	60.6
Pen. with surgery	230	11.3	59.6	70.9	18.7	10.4	29.1
Pen. after surgery	223	9.9	49.8	59.7	19.7	20.6	40.3

penicillin was started and the best results are found in this category. In the last group the penicillin treatment was initiated after the surgery had been done. These groups are not of course strictly comparable. The chief lesson to be learned from the table is that in many cases of surgical infection, surgery may be obviated by penicillin while in others a surgical procedure is required to effect a cure.

The cases have also been divided into three groups according to the method of penicillin administration. The results are shown in Table VI. These three groups are of course not comparable but the table emphasizes the fact that a large proportion of surgical infections may be controlled by the local application of penicillin which represents a very economical method of using the drug.

The question of dosage is an important and a troublesome one. In the

TABLE VI

SHOWING THE RESULTS IN THE THREE GROUPS REPRESENTING THE LOCAL, GENERAL, AND COMBINED METHOD OF GIVING PENICILLIN

Method of Penicillin Administration	Total Number of Cases	Results in Percentage					
		Favorable			Unfavorable		
		Excellent	Good	Combined	Questionable	No Effect	Combined
General, without local	438	16.7	44.7	61.4	20.0	18.5	38.5
Local, without general	142	16.2	54.2	70.4	15.5	14.1	29.6
Both general and local	164	8.5	59.8	68.3	13.4	18.3	31.7

early months of this study the supply of penicillin was greatly limited, the daily dosage was small and it was often stopped as soon as the infection seemed to be under control. Many of these cases had a recurrence of the activity of the infection and required a renewal of treatment. As time went on, more penicillin became available, larger initial doses were given and treatment was prolonged. In many cases large doses were given in conditions where previous experience had shown that small doses would not suffice, or the doses were doubled and doubled again when there was no response to the initial treatment. When a therapeutic agent of low toxicity is available, as with penicillin, the doctor is tempted to use large doses with

TABLE VII

SHOWING THE FAVORABLE RESULTS IN THE CASES ONLY TREATED SYSTEMICALLY, GROUPED ACCORDING TO THE TOTAL AMOUNT OF SYSTEMIC PENICILLIN EMPLOYED

Total Systemic Dosage	Total Number of Cases	Results in Percentage Favorable	
		Excellent	Good
Less than 500,000 units	118	30.5	31.4
500,000 to 1 million	101	18.8	43.6
1 to 2 million	129	12.4	52.7
Over 2 million	90	2.2	52.3

TABLE VIII

SHOWING THE FAVORABLE RESULTS IN THE CASES ONLY TREATED LOCALLY, GROUPED ACCORDING TO THE TOTAL AMOUNT OF LOCAL PENICILLIN EMPLOYED

Total Local Dosage*	Total Number of Cases	Results in Percentage Favorable	
		Excellent	Good
Less than 10,000 units	37	38.0	54.0
10,000 to 50,000 units	40	15.0	55.0
Over 50,000 units	62	4.8	53.3

* Three cases, exact dosage not recorded.

the idea of having a wide margin above the therapeutic level. Any compilation of dosage figures then, may seem to indicate that the worst results are obtained with the largest doses. A prompt response to an initial dose on the other hand, would permit an early cessation of treatment. Thus, the best results might be associated with the smallest total dosage. Certain

of these points are brought out in Tables VII and VIII. It is noted in Table VII that the excellent or prompt response of systemic treatment decreases as the total dose increases while the good results are in the reverse order. Furthermore, the total favorable results decline sharply over the two million mark.

In Table VIII covering the local treatment, one sees that the same decline in "excellent" responses as the total dosage increases while the "good" responses remain stationary. It is of interest that so many cases responded favorably to simple local treatment with relatively small doses given over a short space of time. This group contains, of course, most of the trivial cases and those in which the infection was well-localized.

Have we any criteria upon which we can base the determination of the necessary or adequate dosage for any given case? It is certainly an individual matter. An "adequate" dose is one that will control the infection and get the patient well. The requirements in any given case depend upon the number and susceptibility of the organisms, the extent and penetrability of the local process, the rapidity of absorption and excretion of the drug and the dosage. An "adequate" dose may range all the way from a few thousand to several million units. The experience of the men working in these study units has indicated that a starting dose of 10,000 units every three hours intramuscularly will be adequate in the average case. The intravenous administration is generally not as acceptable to the patient, is harder to administer from a nursing standpoint and results in more rapid elimination of the drug. In a very sick case a large initial dose of 100,000 units may be given, continuing with 20,000 units every two or three hours. With a plentiful supply of the drug and with the danger of developing resistant strains of organisms by inadequate dosage, so feared by Fleming, it would appear reasonable to start routinely with 20,000 units every three hours and double it once if there is no response in 48 hours. There is very little evidence that larger doses will be any more effective than 320,000 units a day in surgical infections. A single daily dose in oil or wax does not give reliable or consistent blood levels.

If there is a response to the initial dosage which clearly indicates the efficacy of the drug it should be continued at that level until one is certain that the infection has subsided with a margin of safety of five to seven days for systemic treatment or two to three days for local treatment. In certain cases with open wounds or ulcers it may be advisable to continue treatment until the wound has healed or is covered by skin grafts or closed by secondary suture.

The most significant features of the study are revealed when we come to the bacteriologic analysis of the flora of the purulent exudates produced in these established surgical infections. In acute infections it is found that the lesions are usually produced by one species of organism but in chronic infections there is often a mixture of organisms, some causative and other "fellow travelers" which have come into the picture as secondary con-

taminants. In this study it was, therefore, necessary to be prepared to recognize and classify any organism both aerobic and anaerobic, pathogenic or nonpathogenic which might be encountered. It was obvious that if the analyses were to be complete, the classification would have to be carried to species recognition. But for purposes of recording, many of the individual species could be put in larger groups. A code sheet was therefore devised and employed so that the results of the study could be adapted to the punch card system for statistical analysis. A copy of this code sheet for bacterial classification is attached to this report. For purposes of final tabulation this classification has been still further condensed into the following significant groups:

1. The hemolytic streptococci.
2. The coagulase-positive staphylococci.
3. The gram-negative aerobic nonspore-forming rods (including *E. coli, A. aerogenes, Ps. pyocyaneus* and *B. proteus*).
4. *Clostridium welchii.*
5. All other gram-negative aerobic nonspore-forming rods.
6. Micrococci, coagulase test not done.
7. Nonhemolytic streptococci (including the green and indifferent types).
8. All other aerobic cocci.
9. Anaerobic and micro-aerophilic cocci.
10. Aerobic gram-positive rods including the large *B. subtilis* and diphtheroid groups.
11. All other aerobic and anaerobic rods.

In one of the units the hemolytic streptococci were grouped according to the Lancefield classification. Most of the strains fell into Group A, confirming the fact that this is the group of human pathogenicity but a number of strains in other groups clearly demonstrated their activity both in pure and mixed cultures. However, a number of the strains were not grouped and for purposes of this report we have, therefore, put them all together. All of the units have confirmed the importance of the coagulase test as an indication of the pathogenicity of the staphylococci but, again, exceptions were found to this rule. This is more important than hemolysis or the finer classification into *albus, aureus* and *aurantiacus* although most of the pathogenic strains were hemolytic and pigmented.

In any case, it is fair to assume that if any organism is found in pure culture in a purulent exudate that that organism is pathogenic and is the cause of the infection. If it is found in a mixture, it may be pathogenic or nonpathogenic, and it may or may not be taking part in the infection. In evaluating the effect of penicillin on these organisms it is necessary not only to put them to the test in the laboratory to demonstrate whether they are susceptible, indifferent or antagonistic to penicillin, but to note whether they were found in pure or mixed culture in the lesion and whether under treatment they persisted into the second or third week of treatment and whether the infection in which they were found responded favorably or unfavorably to the treatment.

Table IX gives the results for the four principal bacterial groups and it is to be seen at once that all of these groups were found more often in bacterial mixtures than in pure culture, the hemolytic streptococci five times as often, the staphylococci twice as often, the gram-negative rods 19 times as often, while the *Cl. welchii* was found alone only once out of 29 times. The table also shows that the favorable response to treatment occurred much

TABLE IX

SHOWING THE RESULTS OF PENICILLIN TREATMENT ACCORDING TO THE PRINCIPAL BACTERIOLOGIC AGENTS ACTIVE IN SURGICAL INFECTIONS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Hemolytic Streptococcus:							
Pure	16	12.5	56.2	68.7	12.5	18.8	31.3
Mixed	85	12.9	49.4	62.3	21.2	16.5	37.7
Coagulase-positive Staphylococcus:							
Pure	47	25.6	61.7	87.3	10.6	2.1	12.7
Mixed	98	10.2	55.2	65.4	23.4	11.2	34.6
4 Principal gram-neg. rods:							
Pure	5	0	40.0	40.0	40.0	20.0	60.0
Mixed	95	1.1	49.5	50.6	25.2	24.2	49.4
Cl. welchii:							
Pure	1	0	100.0	100.0	0	0	0
Mixed	28	7.1	35.7	42.8	32.2	25.0	57.2

more often when the gram-positive organisms were pure than when they were in mixed culture.

The highest percentage of favorable results are found in the pure staphylococcal infections, and this is perhaps the high point of the study which demonstrates that the organism against which Fleming first demonstrated the activity of penicillin is the one which produces the diseases which respond clinically most satisfactorily to treatment with that drug.

Among the gram-negative rods the results in the few cases in which they were found in pure culture, were generally unfavorable. It is not clear why two of these cases gave a good response. There may have been other factors at work in these cases, such as the operative procedure or, by chance, these organisms of relatively low pathogenicity may have been inhibited by the doses of penicillin employed. In the bacterial mixtures containing these organisms they may have been relatively unimportant and in these cases at least not capable of real antagonism against the penicillin which was credited with definite benefit. In the single case in which the *Cl. welchii* was found in pure culture, the result was listed as good but in all of the other cases where it was found in mixed cultures, the response was generally bad. This is a confirmation of the results obtained with cases of gas gangrene in the army. While in experimental animals, penicillin was found to be effective against pure cultures of the gas gangrene organisms, in war wounds, so highly contaminated by bacterial mixtures including gram-negative aerobic

rods, did not do as well as had been expected or hoped for. It is probable that the good results occurred in those cases in which there were no organisms capable of producing penicillinase.

With organisms in the other more or less heterogenous groups, shown in Tables X and XI, the results are not striking. In general, aerobic cocci in pure culture are susceptible while the anaerobic cocci and rods are gener-

TABLE X

SHOWING THE RESULTS OF PENICILLIN TREATMENT IN THE PRESENCE OF ORGANISMS OF LESS IMPORTANCE IN SURGICAL INFECTIONS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
Other gram-neg. aerobic rods:							
Pure	1	100.0	0	100.0	0	0	0
Mixed	29	0	37.9	37.9	37.9	24.5	62.0
Nonhemolytic strept.:							
Pure	10	0	70.0	70.0	30.0	0	30.0
Mixed	109	8.3	43.1	51.4	28.4	20.2	48.6
Gram.-pos. aerobic bacilli:							
Pure	1	0	0	0	0	100.0	100.0
Mixed	102	8.8	56.9	65.8	19.6	14.7	34.3
Staph. coag. test not done:							
Pure	79	30.4	39.3	69.7	12.6	17.7	30.3
Mixed	80	11.2	40.0	51.2	25.0	23.8	48.8

TABLE XI

SHOWING THE RESULTS OF PENICILLIN TREATMENT IN THE PRESENCE OF ORGANISMS OF LESS IMPORTANCE IN SURGICAL INFECTIONS

		Results in Percentage					
		Favorable			Unfavorable		
Diagnosis	Total Cases	Excellent	Good	Combined	Questionable	No Effect	Combined
All anaerobic and micro-aerophilic cocci:							
Pure	2	0	50.0	50.0	50.0	0	50.0
Mixed	54	7.4	50.0	57.4	24.1	18.5	42.6
All other aerobic cocci:							
Pure	18	5.6	61.0	66.6	5.6	27.8	33.4
Mixed	62	4.8	48.4	53.2	30.6	16.2	46.8
All other aerobic and anaerobic rods:							
Pure	2	0	0	0	50.0	50.0	100.0
Mixed	29	0	41.4	41.4	20.7	37.9	58.6
No Cultures:							
Favorable group	37	46.0	37.8	83.8	5.4	10.8	16.2
Intermediate group	16	6.3	68.5	74.8	18.7	12.5	31.2
Unfavorable group	23	4.4	26.1	30.5	30.5	39.1	69.6

ally resistant to penicillin and do not respond, but there are often exceptions to this rule.

In 70 cases no cultures were taken before the administration of penicillin. The great majority of those patients presented early infections in the

stage of cellulitis and there was no opportunity to find out what organism was at fault. If these cases are divided up into three groups according to diagnosis to correspond with the series as a whole, as represented in Tables Ia, Ib and Ic, we find that the results run fairly parallel, so that we may assume that the causative organisms in these cases were roughly similar to those in the whole group, but of this we cannot be certain.

A review of the individual records of the cases in which penicillin was reported to have "no effect" permitted a listing of factors which seemed to be responsible for the failure. These are shown in Table XII. Of the 131 cases in this category, 58 were either infected or contaminated with or-

TABLE XII

GIVING A LIST OF PROBABLE CAUSES OF FAILURE OF THE 131 CASES IN WHICH PENICILLIN HAD NO EFFECT

1. The presence in mixed culture of organisms capable of producing penicillinase			58
Including:			
E. coli	22	*Aerobacter aerogenes*	8
Ps. pyocyanea	18	*Coli* intermediates	3
B. subtilis	18	Other gram-negative aerobic rods	5
B. proteus	15		
2. Tuberculosis			6
3. Tetanus			6
4. Penicillin-resistant staphylococcus			5
5. Penicillin-resistant streptococcus			2
6. Synergism (?) of hemolytic strept. and staph			9
7. Patient *in extremis* on admission			11
8. Too little			9
9. Too late			7
10. Too conservative surgery			9
11. Diabetes and arteriosclerosis			7
12. Metastatic brain abscess, hemiplegia or meningitis			5

ganisms which potentially are producers of penicillinase. In many instances the production of penicillinase was demonstrated in the laboratory. Other causes of failure were the presence and activity or organisms not susceptible to penicillin such as tuberculosis, resistant staphylococci and resistant streptococci. Such overwhelming infections like tetanus and metastatic brain abscess, with hemiplegia or meningitis, often killed the patient before the benefit from penicillin could be appreciated. Diabetes and arteriosclerosis seemed to play a rôle by diminishing the blood supply to the infected part. This prevented the entrance of the penicillin into the focus of bacterial activity as well as the nutritive elements necessary for repair. In some cases too conservative surgery which left behind necrotic bone or other tissue handicapped the effective use of penicillin. In a number of cases penicillin was given in desperation when the patient was *in extremis,* and in a few other cases it could be rightly said that it was given "too little and too late." In a small number of cases there was no obvious cause for failure, nine of these yielded on culture a mixture of *hemolytic Streptococcus* and *hemolytic Staphylococcus aureus.* There may be a synergistic action of these two organisms which is difficult for penicillin to combat.

There were 82 cases in the series with septicemia, eight of these had

more than one organism in the blood stream. These cases have been listed according to the diagnosis of the associated surgical lesion and also according to the bacteriology in Tables XIII and XIV. It is seen that good results were obtained in acute osteomyelitis, suppurative arthritis, cellulitis, a furuncle with pneumonia, a carbuncle and a case of rat bite fever. The *hemolytic Streptococcus* had the best score among the bacteria, with 87.5 per cent good results. The *Staphylococcus aureus* yielded a favorable response in 69 per cent. Before the arrival of the sulfonamides the mortality of *hemolytic Streptococcus* septicemia was in the neighborhood of 50 per cent and of staphylococcus septicemia 80 per cent. We have, therefore, come a long way in protection against blood stream infection with these organisms but

TABLE XIII

SHOWING THE RESULTS OF PENICILLIN THERAPY ACCORDING TO THE ASSOCIATED SURGICAL CONDITION IN THE 82 SEPTICEMIA CASES

	Total Cases	Excellent	Good	Questionable	No Effect
Acute osteomyelitis	21	6	12	1	2
Chronic osteomyelitis	6	0	3	0	3
Suppurative arthritis	6	2	4	0	0
Cellulitis	4	3	1	0	0
Operative wound infection	5	2	2	0	1
Otitis media	2	1	1	0	0
Thrombophlebitis	2	1	1	0	0
Infected rat bite	1	1	0	0	0
Infected burn	4	0	2	0	2
Furuncles and pneumonia	1	0	1	0	0
Carbuncle	1	0	1	0	0
Empyema	3	0	2	0	1
Deep abscess	5	0	2	0	3
Endocarditis	4	0	0	0	4
Peritonitis and perit. abscess	4	0	0	2	2
Miscellaneous	13	1	1	3	8
	82	17	33	6	26

TABLE XIV

SHOWING THE RESULTS OF PENICILLIN THERAPY ACCORDING TO THE BACTERIOLOGY IN THE SEPTICEMIA CASES

	Total Cases	Excellent	Good	Questionable	No Effect
Hemolytic streptococcus	8	2	5	0	1
Staphylococcus aureus	45	11	20	2	12
Staphylococcus albus	6	1	2	0	3
Micrococcus varians	1	0	1	0	0
Nonhemolytic streptococcus	6	0	3	0	3
Anaerobic streptococcus	2	0	0	1	1
Pneumococcus III	1	0	1	0	0
Pneumococcus IV	1	0	0	1	0
E. coli	1	0	0	0	1
B. proteus	1	0	0	1	0
Streptobacillus moniliformis	1	1	0	0	0
Unidentified gram-neg. bacillus	1	0	0	0	1
Staph. aureus and nonhem. strept.	5	1	1	0	3
Staph. albus and nonhem. strept.	1	1	0	0	0
E. coli and *B. proteus*	1	0	0	1	0
E. coli, B. proteus, A. aerogenes, B. subtilis and *Staph. aureus*	1	0	0	0	1
	82	17	33	6	26

our defense is not yet perfect, and when the staphylococcus gets established on the heart valves it is still impossible in most cases to eradicate it. There were no cases, in this series, of recovery after endocarditis had become clinically recognizable.

SUMMARY

The results may be summarized as follows:

1. Penicillin is effective in controlling the disease either alone or as an aid to surgery in about two-thirds of the general run of established surgical infections.

2. It is most effective in cases of furuncle, cellulitis, mastoiditis, carbuncle, suppurative arthritis, lung abscess, superficial abscess, brain abscess, and osteomyelitis.

3. It is moderately successful in cases of deep abscess, thrombophlebitis, sinusitis, infected soft-part wound, infected operative wound, otitis media, infected compound fracture and ulcer of the skin.

4. It is not so successful in cases of empyema, infected burns, gas gangrene, actinomycosis, gangrene of skin, miscellaneous surgical infections, postoperative pneumonia, peritoneal abscess and diffuse peritonitis.

5. It is more successful in the treatment of acute than of chronic infections and if given early rather than late in the course of the disease.

6. It is often effective when the sulfonamides have failed to control the infection.

7. Many cases of well-localized surgical infection can be successfully treated with local injection of penicillin solution or local application of penicillin in ointment form.

8. "Adequate dosage" (which is defined as that necessary to control the infection) may vary from a few thousand to several million units.

9. Surgical infections are frequently caused by mixtures of organisms.

10. Penicillin is not as successful in mixed infections as in those caused by a pure culture of a susceptible organism.

11. Surgical infections caused by a pure culture of a coagulase-positive staphylococcus yield the best results, responding favorably to penicillin in the great majority of cases.

12. The *Clostridium welchii* (the common bacillus of gas gangrene) is so often found in a mixed culture with other intestinal organisms that clinical cases of gas gangrene often fail to respond to penicillin.

13. An analysis of the cases in which penicillin had no appreciable effect reveals the fact that in a large proportion of the cases, the cultures showed organisms capable of producing penicillinase.

14. Other important causes of failure were:

   a. Resistant strains of staphylococci or streptococci.

   b. Too little or too late administration of penicillin.

   c. Associated tuberculosis or diabetes with arteriosclerosis.

   d. Too conservative surgery.

15. In the septicemia cases, the results were better in those due to the hemolytic streptococcus than in those due to the staphylococcus, probably due to the fact that in the latter type the infection more quickly produces deep metastatic abscesses and vegetations on the heart valves.

Four points warrant special emphasis:

1. Penicillin is a very valuable adjunct to surgery in the treatment of surgical infections and in many instances it can obviate surgery, but it is not a panacea.

2. Penicillin is effective when applied locally to well-localized surgical infections if the organisms are susceptible and not antagonistic.

3. "Adequate dosage" is the amount which will bring the infection under control and get the patient well, and it cannot be determined in any given case before the beginning of treatment.

4. A careful and complete bacteriologic analysis is essential to obtain the best results.

COMMENT.—If the bacteriologic analysis of the surgical infection reveals the presence of organisms which are antagonistic to penicillin, some measure will have to be found to offset their action or else the penicillin will not be permitted to inhibit the associated more important organisms. Fortunately, most of the penicillinase producers are relatively nonpathogenic and are not invasive, so that local application of agents which have been found to interfere with their action, may be sufficient to permit the penicillin to function at the site of the infection, whether it is given systemically or locally. It has been found, in these study units, that parachlorophenol in a dosage of .25 of 1 per cent, 9-aminoacridine in a concentration of 1:1000, 5-nitro-2-furaldehyde-semicarbazone in a dilution of 1:1000 and streptothrycin and streptomycin in a concentration of 500–5,000 units per cc. may be successfully employed.

If the resistant or antagonistic organisms are invasive, some agent must be found which will perform this function when used systemically. At present, streptomycin is the only one that we know of that can be used systemically, and is just beginning to be available. There is some hope that new antibiotics will be found which will not have the handicap of inactivation by associated resistant organisms.

Bacitracin, which was discovered in the author's laboratory and is now being developed by a number of commercial firms, is not inhibited by these gram-negative bacteria, although it is not potent against them. It is not yet available in a form suitable for human systemic injection. The author believes that the ultimate control of such mixed infections will come when we can find some chemotherapeutic or antibiotic agent which will destroy or inhibit these second-rate organisms and which can be combined with penicillin for either systemic or local application. These facts are presented with the hope that they may clarify some of the points in the use of penicillin so that it may be more successful in your hands than it has been heretofore.

DISCUSSION.—DR. ALLEN O. WHIPPLE, New York City: I rise to remind the members of the Association of the time when Doctor Meleney was first assigned the difficult task of evaluating the effect of the "wonder" drugs, the sulfonamides, in the healing of wounds. The conditions under which that study was carried out were difficult, because there was a tremendous enthusiasm at that time for the local use of sulfonamides, and when his reports began to appear there was a great deal of bitter criticism and even accusation that the morale of the Army was being disturbed. But it is interesting that, as time has gone on, from various war areas the results which he reported then have been corroborated. And I wish to commend Doctor Meleney for the meticulous care he has used and the fair judgment he has at all times attempted to use in evaluating the effects of these newer chemotherapeutic agents in preventing local wound infection.

DR. JOHN S. LOCKWOOD, New Haven, Conn.: In supplementing what Doctor Whipple has just said, I might remind this Association that just three years ago it was implied by a discusser of Doctor Meleney's paper on wound prophylaxis that those who had participated in the program designed to evaluate the effect of the sulfonamides in wound infection, within five years, would repudiate the preliminary conclusions which Doctor Meleney presented at that time. As a matter of fact, there is now a very general recognition of the limitations in the usefulness of chemotherapy in preventing infections in accidental wounds, and military experience has confirmed the civilian work.

In amplification of Doctor Meleney's interesting report, I would like to suggest that penicillin has stood out as being conspicuously useful in those types of infection characterized by actual tissue invasion by penicillin-susceptible organisms. In types of infection where the infection is more saprophytic in character, penicillin has not been of particularly great value. The infections Doctor Meleney described as being unresponsive to penicillin may have been unresponsive because the organisms are, or have become, penicillin-resistant. But I think it is well to keep in mind the fact that many of the infections in which penicillin was of no value were in wounds of fairly long duration, in which conditions had become ripe for invasion by saprophytic organisms, among them many gram-negative varieties. The lack of effect of penicillin may have been due directly to the resistance of these bacteria but, on the other hand, the poor results may have been inherent in the physiologic character of the wounds. Certainly, the treatment of infections in which penicillin-resistant organisms predominate would seem to be surgical rather than chemotherapeutic. In most of the infections in which one cannot demonstrate the effect of penicillin it is time to undertake surgical revision and skin grafting procedures which, even in the face of superficial infection, can be carried out.

It has been a cause of recent concern to the Committee on Chemotherapy of the National Research Council that penicillin is not a single chemical compound; it is at least four different penicillins known as G, F, X, and K, each with a different chemical constitution. They all possess a strong effect against similar varieties of organisms *in vitro*, and all meet the ordinary methods of bio-assay used in testing. However, penicillin K is a very unsatisfactory penicillin from a chemotherapeutic standpoint. It is rapidly broken down in the body; it is all gone within 30 minutes. This is of some practical importance, because it is thought that a good deal of the penicillin distributed has contained as much as 60 per cent penicillin K, and there is reason to believe that some of the spotty clinical results have been due to penicillin K in commercial penicillin. This has been called to the attention of the manufacturers, and the problem will now be remedied, but for six months to a year there has been a good deal of penicillin K in circulation. This provides a basis for explaining some of the discrepancies in results in penicillin treatment. We hope it will in the future contain 80 to 90 per cent penicillin G, or other penicillin of known value, so that penicillin K may be eliminated as a possible source of poor results.

DR. JONATHAN E. RHOADS, Philadelphia, Pa.: I wish to congratulate Doctor Meleney on assembling this very complex group of data and presenting them so concisely. It is somewhat surprising that the poorest results in the entire series were observed in spreading peritonitis. We did not have very much confidence in the drug in treating peritonitis so we did not at first include these cases in the clinical study carried on in Philadelphia. However, certain animal experiments were undertaken. Dr. John Murphy, Dr. Robert Ravdin and Dr. Harold Zintel produced experimental peritonitis in dogs by the method of Poth. In a small series they obtained a 70 per cent survival when penicillin was administered.

Miss Ann Nichols in our laboratory has obtained some evidence that in mixed infections, of which peritonitis is an example, you may get a synergistic effect between penicillin and streptomycin. Since some organisms are susceptible to one and some to the other, it is not surprising that mixed cultures may be inhibited more effectively by small amounts of each drug than by either one alone.

In another series of animals studied by Doctor Zintel, and his associates, in which peritonitis was produced by ligating the appendix and its mesentery, the combination of penicillin and sulfonamides resulted in a slightly lower mortality than did streptomycin alone. Experiments are now in progress combining streptomycin with the other drugs, and the mortality is running at a still lower rate.

Again I want to thank Doctor Meleney for putting these data in so useful a form.

DR. FRANK L. MELENEY, New York City (closing): Time did not permit me to pay adequate tribute to those who contributed to this study. I would like to mention besides Drs. Harold Harvey and Robert Elliott, Drs. John Lockwood, William White and Jonathan Rhoads, in Philadelphia, William Altemaier, in Cincinnati, John Hirshfeld, Roy McClure and Conrad Lam, in Detroit, and Alton Ochsner and Guy Caldwell, in New Orleans, all of whom contributed largely to this work by sending in their case records. From these we have derived our data. I am glad that Doctor Lockwood emphasized the possibility of other factors operating, when penicillin has failed. All these factors have been mentioned, but in going over these cases with great care there was a large number (58) in which the cause of failure seemed to be the presence of those organisms which are capable of producing penicillinase. When such surgical infections are under treatment there should first be a careful bacteriologic analysis of the wound. Then each and every strain of organism should be tested both for susceptibility and for antagonism to penicillin. If antagonistic species are found some measure must be found to inhibit their activity. Most of the penicillinase-producing species are nonpathogenic, so that local agents which interfere with their growth may be sufficient to permit penicillin to function against susceptible pathogens at the site of infection. We have found that 1-400 parachlorophenol is one of the most potent antibacterial agents against these penicillinase-producing gram-negative bacteria, and in that concentration it is not toxic when applied locally. Streptothyrcin and streptomycin in concentration of 500-5,000 units per cc. may be employed locally if the organisms are susceptible to them. At present, streptomycin is the only one of the potent antibacterial agents that can be used systemically, and that is sometimes toxic. It is hoped that new antibiotics will be found that will not be inhibited by either injured tissue or bacteria, the chief inhibitors of the sulfonamides and penicillin, respectively. Such a chemotherapeutic or antibiotic agent might then be combined with penicillin to render it more effective in the treatment of established surgical infections due to a mixture of organisms. Bacitracin may fall into this category.

THE CLINICIANS' RESPONSIBILITY IN THE TEACHING OF SURGERY*

ALBERT O. SINGLETON, M.D.

GALVESTON, TEXAS

THE METHODS of teaching medicine are ever changing and have been as far back as the history of medical education goes. No other subject of American education has been so drastically reformed in so short a time.

From a surgical standpoint scientific medicine began with the science of *anatomy* sponsored by Vesalius. Then with the advent of Harvey the science of *physiology* was added, and led by Morgagni, *pathology* was added. Soon there developed from anatomy, *histology* and *embryology,* from physiology, *biochemistry,* and from pathology, *bacteriology.* Thus, we see how it has been necessary with the great amount of increasing knowledge in front of the student, for the plan of teaching as well as the type of teachers, to change.

Clinicians in the past were the teachers of the fundamental subjects and medical students, therefore, had the subjects presented to them with their clinical application always before them. On the other hand, busy clinicians could give little effort to research and the development of the true science of these subjects. A change was inevitable and the medical schools were the natural institutions for this effort. Thus, the result was that the research teacher gradually replaced the clinical teacher. To medical faculties were added scientists who were specially trained in the true science of medicine.

During the past 25 years the clinical teachers have been gradually replaced by the pure science teachers and the once close association between the clinical and fundamentals has gradually grown wider, and, as stated by Cropper: "It would seem that the medical schools should steadfastly set their faces against their preclinical teaching, remaining solely in the hands of the pure scientists. Pure scientists in any branch of the subjects tend to demand from the student a far too detailed knowledge of the branch."

Also, it may be true that the standards of medical education and the accepted curricula of medical schools by committees on medical education are largely the results of the opinions of teachers of fundamental subjects rather than the clinicians. This situation is quite different from that in the beginning (1904) when the Council on Medical Education of the American Medical Association started to function under the able leadership of the distinguished clinical teacher of surgery, Dr. Arthur Dean Bevan.

It has seemed wise and perfectly natural with the advance of the many full-time preclinical science teachers, that from this group deans and other

* Presented by title before the American Surgical Association, April 2–4, 1946, Hot Springs, Virginia.

administrative officers of medical schools should be selected. Though the membership of the Association of American Medical Colleges includes all members of medical faculties, it is the administrative officers of the medical schools who actually carry on the good work of the organization. We must admit the tremendous value to medical education of this organization, but is it not possible the criticism we may have of the modern undergraduate teaching may be attributed to the difference in viewpoint of the teachers of the fundamental subjects and that of the teachers of the clinical subjects? No one can deny that, in general, scientific advancement which is for the good of the patient has been due to our modern methods of teaching, but this does not prevent us from finding fault with the system. It may be that scientific advancement is carried on in some respects at the expense of the best interest of the graduate in medicine.

No article in regard to medical education should be complete without a reference to a brilliant contribution by a great clinical teacher — Dr. David Cheever, read before the American Surgical Association, in 1933, under the title of "Anatomy Eclipsed," who says: "If the systematic instruction is given by a professor who has no clinical experience, who knows only from hearsay — if at all — and is not concerned with the reasons why anatomical facts are of importance to the practicing physician or surgeon; whose real interest and enthusiasm lie in the field of comparative morphology or experimental embryology, it can scarcely be expected that the subject shall be presented in a stimulating, interesting and profitable manner. It is unwarrantable to assume that junior instructors, teaching in sections, ill-paid and lacking in experience as teachers, will assure the entire class of receiving what they ought to get from a senior member of the department."

Dr. Cheever states further: "The teaching of anatomy is under the direction of the laboratory assistants generally, who hold no degree in medicine and have no clinical experience. Doctors of Philosophy, Bachelors of Science to a considerable extent are responsible for the teaching of fundamental subjects in the American medical schools."

Dr. Harvey Cushing, the famous clinical teacher, has stated: "More and more the preclinical chairs in most of our schools have become occupied by men whose scientific interest may be quite unrelated to anything that obviously has to do with Medicine, some of whom, indeed, confess to a feeling that by engaging in problems that have an evident bearing on the healing art they lose caste among their fellows." "It tends to create a sense of frustration in the morphologic and clinical anatomist to learn from the pen of the Professor of Anatomy in one of our most conspicuous and richly endowed schools that the subject of the former's study and teaching is nothing but "fixed protoplasm," that "Human anatomy was in great danger of becoming nothing more than a handmaid to Medicine and Surgery" — and that "the days when the anatomist commanded the respect and confidence of his medical colleagues solely on the basis of his knowledge of static morphology, are rapidly disappearing."

Quoting again from Dr. Cheever: "It is unreasonable to declare that gross descriptive morphologic anatomy is unworthy of being taught by a man of seniority and experience in teaching, of wide clinical experience, preferably in surgery, and of broad interests in the whole field of medicine, especially the fundamental subjects." "Let us believe that the prime duty of the medical school is to prepare men to practice the art of preventing and healing disease and let us consider that duty as out-ranked in dignity and importance to no other on earth."*

Standardizing committees realizing this deficiency have endeavored to compensate by recommending correlating lectures for the first and second year classes by members of the clinical staff upon the subjects of anatomy, physiology, biochemistry, *etc.* These lectures are irregular, not systematic and serve only as entertainment for the student, I am afraid, and fall far short of the objective which they are expected to reach.

In the institution with which I have been connected for the past 35 years (the University of Texas), surgical teaching began following closely the British schools, in which the fundamentals of anatomy, pathology and physiology were the attracting center, which were ever emphasized in the fundamentals of surgery.

The present curricula of surgical teaching in the modern medical school has tended to draw away from these basic subjects and we have had considerable misgiving in giving our consent to the giving up of many hours of instruction in them. This situation has been more difficult for us to accept because of the previous facts which we have endeavored to bring out showing that the clinical teachers no longer have a part in the teaching of these fundamental branches, which has naturally resulted in the student coming to his junior year without having had the clinical viewpoint to show him the use to which the fundamental knowledge may be used in clinical work for the good of the patient. Because of this state of affairs we have felt more and more that the surgical departments should spend considerable time in teaching applied physiology, applied or surgical anatomy,† and surgical pathology. Our former extensive course in surgical anatomy has been reduced greatly but is still taught in the senior year. Time allotted to classes in surgical pathology has been greatly reduced but we have been able to retain some 32 hours per student in the senior year, and physiology, which we have attempted to teach with experimental or animal surgery, is given in the junior year occupying some 22 hours.

Believing very strongly that a weakness exists in present teaching methods, and also knowing the unpopularity of the above subjects with standardizing committees on curricula of the American Medical Association and the Association of American Medical Colleges, we have endeavored to secure the opinion of the teachers of surgery from medical schools in America

* Though the teachers of anatomy in our school are Ph.D.'s they are high in rank and do the direct teaching of the subjects.

† Thirty hours have been allowed for this year.

in appraising these problems. Replies to a letter requesting opinions were received from 60 professors from 40 medical schools of the United States and Canada. Those who replied showed the same discontent in regard to their present methods of teaching and uncertainty as to the teaching schedules which should be maintained.

SURGICAL ANATOMY

Thirty-five of the 40 medical schools continue teaching surgical anatomy. Five had discontinued the teaching of surgical anatomy. The number of hours given to surgical anatomy varied from 20 hours to 50 hours, and the great majority expressed strong convictions that surgical anatomy should have a place in the undergraduate medical school curricula and be taught by highly experienced and trained surgeons.

Dr. I. A. Bigger, of the Medical College of Virginia, says: "We had to give up for the time-being our course in surgical anatomy. I am extremely sorry this had to be done and we do plan to again develop such a course when we have an adequate staff."

Dr. Warren H. Cole, of the University of Illinois, states: "We devoted 48 hours total to surgical anatomy. I am personally convinced that we should not abandon our course in surgical anatomy, even though the student is not going to be a surgeon. He forgets so much anatomy that the course in his junior or senior year, which would correlate anatomy with a surgical approach, should be a method of making the dry facts stick a little better in the student's memory."

Dr. Loyal Davis, of Northwestern University, says: "We give a class in surgical anatomy to the senior medical students. They are given cadavers to dissect. The class is taught by a surgeon who has, in the past, demonstrated his ability to teach gross anatomy and a man who is much interested in his class. It is given to about 40 students for four hours a week for one quarter, that is, 12 weeks."

Dr. J. Stewart Rodman, Woman's Medical College of Philadelphia, says: "I am glad to learn that you are holding on to surgical anatomy and are giving it to your senior students in a course lasting from 18 to 20 hours to one-third of the class at a time. I believe that surgical anatomy should be taught by surgeons and not by the Anatomic Department. We have followed this plan with success in our own teaching."

Dr. Alfred Blalock, of Johns Hopkins Hospital, says: "I feel very strongly that surgical anatomy is well worth while."

Dr. Dan Elkins, of Emory University, says: "I have long been of the opinion that so much extraneous matter is slipping into the curriculum that our students are graduating with a poor basic and fundamental medical background. I sometimes think it would be better if we went back to the old system where anatomy was taught by surgeons. No undergraduate medical student can master all of anatomy, but a good anatomist who is also a good

surgeon can stress the importance of certain anatomic structures and relationships, a thing which is not done by the so-called pure anatomist."

Dr. Frederick A. Coller, of the University of Michigan, says: "We give 22 practical regional studies on a cadaver, and each laboratory period is preceded by a demonstration stressing the surgical aspects of the region under consideration. Although it is an elective course, 90 per cent of the students take it."

Dr. Edwin P. Lehman, of the University of Virginia, says: "We give a rather extensive course in surgical anatomy. The value of this course is to me very great. The record of Virginia students in state board examinations in anatomy has been greatly improved since this course was initiated. It is my conviction that anatomy learned after clinical contact is going to be retained much better than anatomy learned as a pure science."

Dr. Allen O. Whipple, of Columbia University College of Physicians and Surgeons, says: "We have experienced the curtailment in our medical school curriculum of the teaching hours in anatomy and pathology, but both these basic subjects are essential to the teaching of surgery. We also give a course in regional anatomy to our third year surgical clerks, covering the neck, the extremities, the chest and abdomen. I have conducted the exercises in the abdomen for a number of years. In this course we emphasize the surgical significance of anatomic structure, but we do not use the course to teach surgical technic."

Dr. John Morton, of the University of Rochester School of Medicine and Dentistry, says: "We give a course in surgical anatomy in the senior year, also give correlation courses to the first-year students. In the first year we give clinics illustrating the importance of anatomy. This is to demonstrate to the students some of the reasons why they study the muscle origins, insertions, *etc.* We present such things as poliomyelitis, paralysis, nerve injuries, congenital defects, *etc.* This exercise occurs once a week during their anatomic course. At the end of the second year we teach physical diagnosis along with the medical people, but we teach it from a surgical standpoint. That includes methods of diagnosis of ear, nose and throat, neck, thyroid, and the breast which they do not get on medicine, orthopedic examinations for joints, spine and feet, urologic and rectal. All these methods of examination are taught by the surgical department, also a complete neurologic examination and blood vessels."

Dr. Alton Ochsner, of Tulane University, says: "I think it has been perfectly all right to reduce the number of hours given to anatomy, since the older curricula were top-heavy with anatomy. On the other hand, I think it is desirable to give some anatomy in the clinical years. We give a course in surgical anatomy, which is probably not as elaborate as yours. It consists of demonstrations, on presected bodies, of regional anatomy. This is given by members of the surgical staff once a week to a third of the class at a time, for a period of one-third of the year and is given in the Junior year. I believe that the students get a great deal out of it, and it is also valuable to

the staff since it gives them a chance to review their anatomy by presecting the bodies."

Dr. Owen H. Wangensteen, of the University of Minnesota, says: "It would be a good plan to reduce the number of hours in preclinical years, bringing the student into the clinical years at an earlier date; then, to give the students in the third and fourth years additional training in anatomy and pathology. I think this is sound. The anatomists obviously do a good job in absorbing the difficult shock of initiating the medical students into the discipline of hard study. I think it would be sound to return to the plan as stated above. We do give a course called "Applied Surgical Anatomy" and I think they get a good deal of good out of it."

Dr. Dallas B. Phemister, of the University of Chiçago, states: "I am in favor of a course in surgical anatomy for seniors. This course consists of lecture demonstration of the surgical anatomy of a field followed by student operations of the cadaver. Though it is elective the success of the course is inferred by the fact that at least four-fifths of the class take it and I think it is worth while."

Dr. Erwin R. Schmidt, of the University of Wisconsin, says: "I am afraid that I am still a little old fashioned and believe that surgeons have to be thoroughly grounded in surgical anatomy, pathology and dog surgery. These things to me are fundamental principles upon which a surgeon must build. I feel the way you do — that I do not want to become inflexible and not accept new methods; but I have reached the stage that after these things are taken care of; namely, surgical anatomy, surgical pathology and dog surgery, then I am open-minded, and I would be very loath to change my ideas."

Dr. Thomas G. Orr, of the University of Kansas School of Medicine, says: "I am much interested in the teaching of surgical anatomy. After all the criticism of the teaching of anatomy by anatomy instructors which has appeared in the literature, I am still of the opinion that they do a very good job. The teaching of anatomy as applied to clinical medicine, is in my opinion, strictly a responsibility of the clinicians, preferably in the senior year. The modern clinician should be able to emphasize in his teaching anatomy, pathology, physiology and biochemistry. At present we have only one short course of 12 weeks in surgical anatomy. This is hardly enough but it is the best we can do with our crowded curriculum. Teaching in medical schools seems to be a very popular subject for discussion at present. Some of the discussions appeared to me to be rather visionary, particularly those which placed so much emphasis upon the correlation of the preclinical subjects with clinical subjects. It is my firm belief that preclinical laboratory men are usually not competent to teach correlation courses, and here again such teaching must be largely delegated to up-to-date clinicians. I believe some of our younger men may be more competent to emphasize such subjects as physiology and biochemistry than our older men."

Dr. David Cheever, of the Peter Bent Brigham Hospital, Boston, says:

"I think you would be interested in an article of mine entitled "Anatomy Eclipsed" in the ANNALS OF SURGERY for October, 1933, and contained also in the transactions of the American Surgical Association for that year. I have not changed my opinions then expressed, and will only repeat that I think it is most unfortunate that the teaching of gross anatomy is largely turned over to Ph.D.'s and other persons who have no knowledge of surgery or medicine. Please read it."

Dr. W. D. Gatch, of the Indiana University Medical Center, states: "I regard your plan of teaching surgery as essentially sound. I believe that teaching should be built around anatomy, pathology and applied physiology."

SURGICAL PATHOLOGY

In reply to the question of the value of the teaching of surgical pathology, the answers were almost 100 per cent in the affirmative. Many of these replies were to the effect that surgical pathology should be taught in the Department of Surgery — again, in order that the student might get the clinical viewpoint and correlation of the pathologic picture with the clinical. In fact, it occurs to us that the strongest surgical departments with which we are acquainted, lay great stress upon this arrangement.

Dr. Evarts Graham, of Washington University School of Medicine, says: "I have had the conviction for a good many years that the emphasis in the surgical teaching of undergraduate students should be placed largely in the diagnosis of surgical conditions, the teaching of what can be accomplished by surgery in various disorders, the principles of postoperative care and all of those things which go to make up the complicated picture of disturbed physiology in connection with surgical disorders and a *great deal of emphasis on surgical pathology. Here the Department of Surgery gives all the instruction in surgical pathology.* I believe it is a good thing to emphasize in the student's minds the fact that no one can be a really good surgeon unless he is a good pathologist. The fact that we do stress pathology so much here has its effect on all of the young men who are taking graduate work in surgery."

Dr. J. Stewart Rodman says: "From my experience with the American Board of Surgery I would say that there can be no more sound approach to surgery than through anatomy and pathology. These are the only two basic sciences in which a special examination is given."

Colonel Daniel C. Elkins, of Emory University, says: "I have been particularly impressed since I have been in the army with the lack of knowledge of anatomy and pathology on the part of recent medical graduates. We have had three or four groups of some 30 men who have been sent here for three months training. They come from all schools in the country, and very few of them have a basic conception of what these subjects mean in relation to clinical practice. Day in and day out we have to expose large vessels and large peripheral nerves, and their ignorance concerning these matters is appalling. The board members of the American Board of Surgery

were so impressed with the lack of knowledge of anatomy and pathology that one of its members — Dr. Allen O. Whipple — was induced to address the Association of American Medical Colleges on this subject. I am afraid he did not get very far."

Dr. J. Deryl Hart, of Duke University, says: "It has been a source of considerable concern to me that we have not had a course in surgical pathology. Our surgical pathology is handled by the Pathologic Staff, and they have not felt they were in a position to offer such a course. After the war we plan to have a surgical pathologist who will be jointly responsible to Surgery and Pathology, and he will have a course in surgical pathology."

Dr. Erwin R. Schmidt, of the University of Wisconsin, says: "We give 32 hours of surgical pathology to junior students; in addition, in the senior year, surgical pathology is taught throughout the year in a surgical pathologic conference which is held once a week."

ANIMAL OR EXPERIMENTAL SURGERY

Sixteen of the 40 schools have classes in animal surgery. In regard to the teaching of animal surgery, the answers indicate that about one-half of the schools conduct such classes and about one-half do not. The expressed opinions vary considerably in regard to the value of such teaching. There was rather universal opposition to teaching surgery in the strictest sense on animals. Those who favored such a class emphasize that its value was to teach asepsis, tissue handling and hemostasis, as well as demonstrating physiologic principles, or a correlation course in physiology conducted upon animals. Many were outspoken in opposition to such classes, others were favorable.

Dr. Barney Brooks, of Vanderbilt University, states: "As to animal surgery, we formerly had a required course (one year) one afternoon each week for all the students in the third year class. I must confess that although the students always expressed a very great amount of enthusiasm for this course in animal surgery, I had a considerable amount of question in my mind as to whether it was worth while or not. At least about five years ago we changed the course to an elective course, but I believe nearly all the students elected to take it. During the past three years the course has been discontinued entirely, not only because of the shortage of our teaching staff, but also because of the shortage of animals and because of our inability to obtain janitors for the preparation of the materials used."

Dr. Loyal Davis states: "We discontinued a class in animal surgery because we felt it was a waste of animals and the men learned nothing, but even more important, we believe that surgical technic should not be taught until the man goes into the hospital as a clinical clerk or intern. We teach them aseptic technic when they are clinical clerks and each one of the senior students has a clerkship in surgery."

Dr. Evarts Graham states: "We gave up our course in dog surgery five or six years ago. I think it has some value in teaching the importance of

asepsis and the gentle handling of tissues but yet I think it has also certain very great disadvantages. I could not help feeling that the course had two results which were harmful. One was that it overemphasized the technic of operative surgery and, in the second place, that it gave the students the idea that surgery is much easier than actually it is. The ease with which almost any operation can be carried out on a normal dog is so different from that experienced on the human being with marked local pathologic changes, together with the fact that the patient may be a poor risk anyway, created a false impression that the removal of a gallbladder, the resection of a stomach, or a thyroidectomy, was a very simple procedure. However, the giving of the course is such a big job that I seriously question whether it is worth the labor put into it, aside from the actual harm that it may do."

Dr. Frederick A. Coller says: "We also give a course in the surgical laboratory to work on animals. With us this is given in the senior year and we likewise give it to stress the handling of tissues, aseptic technic and to some degree anesthesia. We make no attempt to teach them in any detail the various operations of surgery at that time."

Dr. Howard C. Naffziger states: "As to animal surgery, we would prefer to give it in the third year, but because our students are not at the University of California Hospital during that year, we give it in the fourth, and I imagine give the same sort of course that you do. They receive instruction in anesthesia, the duties of a scrub nurse, methods of cleaning up, wound healing and the use of the different kind of sutures, *etc.*"

Discussion.—From the foregoing information we can correctly state that it is the opinion of the clinical teachers of surgery in America that the curricula of medical schools should require:

1. *Surgical Anatomy:* The teaching of surgical anatomy by clinical surgeons during the junior, or preferably the senior year of medical school. This teaching should be done when possible by those of higher rank and experience in the surgical departments. The number of hours devoted to this teaching should be not less than 20, and preferably 40.
2. *Surgical Pathology:* Surgical pathology should be reviewed and greatly emphasized in the senior year. Gross and microscopic pathology, particularly that of neoplasms, should be given 40 to 50 hours. These subjects should be taught by well-trained pathologists jointly with the clinical teachers of surgery.
3. *Animal Surgery:* The teaching of applied physiology in the animal laboratory work, though not essential in the undergraduate curricula, may be advisable. The principles and practice of aseptic technic may be taught to advantage. This work probably should be given in the junior year and before the student enters the operating room. Aseptic technic may be learned, as well as the methods of handling tissue, ligating vessels and the use of sutures. Also, it may be that some of the students becoming familiar with the management of animals and

laboratory technic, will be encouraged to do research work in the future. The combining of the teaching of anesthesia with surgery in the animal laboratory gives an opportunity for demonstrating the physiology of respiration, fundamental principles of open chest operations, as well as a greater knowledge of anesthesia in its physiologic application.

Finally, it is the duty of the clinical teachers of surgery to take more interest in the work being done by the Association of American Medical Colleges and the Committee on Medical Education and Hospitals of the American Medical Association. Attendance upon the meetings of these organizations and expressing opinions in regard to undergraduate teaching would be welcomed by the accrediting bodies and would result in a teaching program more acceptable to clinical teachers, as well as those of the fundamental subjects.

REFERENCES

[1] Cropper, C. F. J.: Preclinical Years: With Special Reference to Teaching of Physiology, British Medical Journal, **1**, 389, March 27, 1943.

[2] Cheever, David: Anatomy Eclipsed. ANNALS OF SURGERY, **98**, 792–800, 1933.

ANNOUNCEMENT

DR. ALLEN O. WHIPPLE, Valentine Mott Professor of Surgery at Columbia University and Director, Surgical Service, Presbyterian Hospital, has accepted a position on the medical faculty of the American University of Beirut.

Announcement of Doctor Whipple's plans was made by Albert W. Staub, American Director of the Near East College Association. Doctor Whipple, who retires September 30th this year, after 35 years on the Columbia Medical faculty and 34 years at the Presbyterian Hospital, will leave for Beirut, Lebanon, late in September.

"Doctor Whipple, one of America's great surgeons, will advise on the development of the new medical center of the American University of Beirut," Mr. Staub said. "As a trustee of the university he has helped plan the new teaching hospital at Beirut, one of the pioneer medical centers in the Near East where more than one thousand doctors have been graduated since 1867."

Doctor Whipple, a graduate of Princeton and Columbia, has specialized on surgery of the pancreas and spleen. During the war he was chairman of the subcommittee on infected wounds and burns of the National Research Council, Fellow of the American Academy of Surgeons, editor and author of medical treatises and books, and officer of several medical and surgical organizations.

NEAR EAST COLLEGE ASSOCIATION, INC.
46 Cedar Street, New York 5, N. Y.